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Editorial

THE IMPORTANCE OF THE SHAPE AND SIZE OF THE HEART

A GREAT deal of attention has been given to the dilated heart, in connection with Starling's law and with heart failure. The effect of changes in length of the cardiac fibers of the ventricle upon their force of contraction, i.e., Starling's law of the heart, is well taught to students. However, there is another way in which the diastolic size of the heart greatly affects cardiac function, which is seldom taught and is, perhaps, not clearly understood even by the readers of this journal. This is the effect of its size and shape upon the simple mechanics of the operation of the heart, i.e., the relation between the force developed by the ventricular muscle in contraction and the pressure generated in the ventricle.

Burch[1-3] and several others have written on this matter, making the same points that are emphasized in this article. However, the physical relations have been given in mechanical formulae that are, strictly speaking, limited in application to "spherical" hearts, although the result applies to a heart of any shape. Perhaps there is little to be gained, in explaining the matter to the non-physicist, by adopting approximate formulae of this type rather than going directly to the heart of the matter, the general law of Laplace, which enables us to understand the role of both the shape and the size of the heart. The consequences of applying this law to the heart, particularly as to its oxygen requirement, are still not generally appreciated, in spite of the excellent articles by Burch and his co-workers.

Yet the application was made lucidly and most interestingly as long ago as 1892,[4] by R. W. Woods, who was a throat surgeon and demonstrator in anatomy at Trinity College, Dublin. Since our laboratory has successfully applied the same law of Laplace to the cylindrical blood vessels,[5] I may be permitted to repeat what was said more than 60 years ago as to the application of the same law to the two noncylindrical blood vessels which are the cardiac ventricles. I should very much hope that Woods' paper would be accepted today, with little modification, if it were submitted for publication, but this is not likely to happen.

Woods' paper is entitled "A Few Applications of a Physical Theorem to Membranes in the Human Body in a State of Tension," and he applies Laplace's law not only to the ventricles of the heart but also to the urinary bladder and to the uterus. His "physical theorem" is the law of Le Marquis de Laplace, that

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curious mixture of mathematical-physical genius and self-seeking politician who dominated the mathematical world in the century following Newton. (He completely excluded from his publications all references to the work of his predecessors and contemporaries.) The theorem appeared first in Laplace's *Mechanique Celeste*, the volumes of which were published between 1790 and 1825.

THE LAW OF LAPLACE

The theorem of Laplace applies to a "membrane" separating two spaces, of any shape, that has a "tension" in it. By this is meant that if a slit were cut in the membrane, the two edges of the slit would pull apart with a force of a certain number of dynes per centimeter length of slit. The wall of the ventricle is such a "membrane," and in the contraction phase a slit in the ventricle wall would so pull apart. The tension in the membrane is denoted by T dynes/cm. length of slit. There is also a difference of pressure across the membrane, i.e., between "inside" the ventricle and "outside." This is denoted by P dynes/sq. cm. (1 mm. Hg = 1,330 dynes/sq.cm.). In systole P will equal the ventricular systolic blood pressure. Now, the law of Laplace states that the difference of pressure P and tension T must be related by an equation involving the *shape* of the membrane (its "principal radii of curvature"). This equation is:

Equation: $$P = T\left(\frac{1}{R_1} + \frac{1}{R_2}\right) \tag{1}$$

Units: $$dynes/sq.\ cm. = dynes/cm. \times \left(\frac{1}{cm.} + \frac{1}{cm.}\right)$$

R_1 and R_2 are the "principal radii of curvature" at any point on the membrane. To explain these radii in general is difficult and involves "plane" diagrams that are difficult to visualize in three dimensions. It is better here to explain the matter with direct reference to what Woods did on hearts from necropsy. Perhaps some readers will be reminded of their first year college physics, if it is pointed out that for the special case of a spherical membrane, where the radii of curvature are equal ($R_1 = R_2$), the general equation "degenerates" into:

$$P = \frac{2T}{R} \tag{2}$$

This is familiar as applied to soap bubbles. For another special case, for cylindrical vessels, one of the radii of curvature is infinite, since the wall of a cylinder is "flat" in one direction (parallel to the axis of the cylinder), so that,

$$P = \frac{T}{R} \tag{3}$$

Equation (3) is the one we have applied to the blood vessels to predict their instability at low pressures, and the existence of "critical closure."

Woods took necropsy hearts, "dilated the ventricles with spirit under a head of about 12 in." (this would be a pressure of about 17.5 mm. Hg), and left them until they hardened. He then chose a number of points on the surface

in which to stick pins in order to represent the "normal" to the surface at those points (such as at *P*, Fig. 1). At such a point on the surface, two lines, APB and CPD, can be drawn at right angles to each other, representing the "principal lines of curvature" at that point. In the case of the heart wall, which is approximately a surface of revolution, one of these lines (APB) will be approximately horizontal, i.e., at right angles to the axis of revolution, the other at right angles to this. Then, somewhere on the normal (broken line produced back into the heart) there is a center of curvature, O, where one leg of the compasses can be put so that the other leg closely describes the arc APB. There is another center of curvature, O′, also on the normal, where one leg of the compasses can be put, so that the other leg will describe the arc CPD. The distances OP, O′P are the two "principal radii of curvature" of the heart wall at the point P. The arcs APB and CPD were chosen instead of *any* two arcs at right angles because any other pair of arcs would give two *other* centers of curvature and two other radii of curvature. The "principal" radii of curvature are the maximum and the minimum radii of curvature that we would find if we tried all the possible pairs of arcs like APB and CPD. (For further explanation, the textbooks must be consulted.)

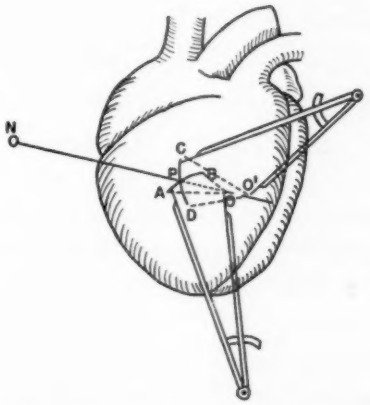


Fig. 1.—Illustration of the principal radii of curvature at a point P on the ventricular wall. *N P O O′* = "normal" at *P*. *APB* and *CPD* = principal lines of curvature through *P*. *O* and *O′* on the normal = centers of curvature. *OP* and *O′P* = principal radii of curvature.

Woods estimated the radii of curvature for each of his chosen points. He then assumed, reasonably, that the thickness of the ventricular wall at any point should be proportional to the tension that the wall could develop in systole, i.e.,

$$T = kt \qquad (4)$$

where k is the proportionality constant, that is, the tension per unit thickness of wall. Then equation (1) becomes:

$$P = kt\left(\frac{1}{R_1} + \frac{1}{R_2}\right) \qquad (5)$$

If this equation were true, $t\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$ should be much the same for all the

points he had chosen on the wall for the right ventricle, and similarly constant (but with a different value because the pressure P was lower) for all points on the right ventricle. His results are reproduced in Table I.

The agreement with expectation is quite remarkable. The constant (0.055) for the right ventricle is about one sixth of that (0.36) for the left ventricle, as it should be, since P for the left ventricle is about 125 mm. Hg, and for the right, 25 mm. Hg.

We see how the law of Laplace explains the great variation of thickness of the ventricular wall. In the very much curved parts of the ventricle, as at the apex, the wall can be thin and still produce sufficient tension to develop enough pressure in the contents, because the tension is at a "mechanical advantage." When the wall is "flat," as it is midway up the ventricle (Fig. 2), the tension developed must be much greater to produce the same pressure; so, the wall must be correspondingly thicker. From this we see that the wall of the right ventricle is much thinner than that of the left, since the pressure to be developed is a great deal less.

The same law must apply to the arch of the aorta (Fig. 2). Here the radii of curvature on top of the arch are like those of the ventricular wall, i.e., the centers of curvature are on the same side of the surface. But below the arch

TABLE I. ADULT HEART (NORMAL)

LABEL OF POINT CHOSEN	r MM.	r_1 MM.	t MM.	$t\left(\frac{1}{r}+\frac{1}{r_1}\right)$
Under Pressure 12 in Right Ventricle				
z_1	60	60	1.5	.050
c_2	65	80	2.0	.055
d_2	32	75	1.25	.055
a_2	75	90	2.2	.054
e_2	30	45	1.0	.055
f_2	55	90	2.0	.058
				Average .0545
Left Ventricle				
p_1	36	60	8.0	.35
z	32	80	8.5	.37
x_1	70	36	9.5	.39
r_1	30	80	8.5	.38
o_1	28	60	7.0	.36
s_1	70	40	8.5	.33
m_1	80	40	10.0	.37
w_1	32	80	8.5	.34
f_1	55	16	5.0	.40
t_1	70	24	6.0	.33
v_1	24	70	6.5	.36
n_1	60	24	6.0	.35
				Average .36

the curvatures are opposite in sign. Such a surface is called "anticlastic"; where the centers of curvature are on the same side, the surface is "synclastic." Here the $\frac{1}{R_1}$ and $\frac{1}{R_2}$ are of opposite sign, and subtract in the equation, instead of adding together. The result is that for the elastic tension in the wall to withstand the aortic pressure, the thickness of the elastic tissue must be much greater on the inside of the arch, where the wall is almost "flat," than on the outside where it is very much curved. Fig. 2 shows that this is actually the case, as I have found in the aorta of rabbits and cows.

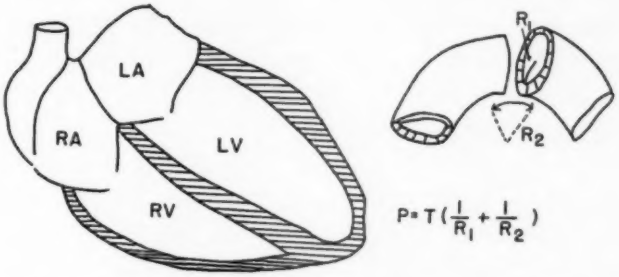
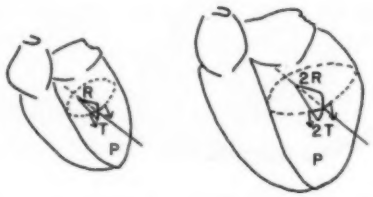


Fig. 2.—Law of Laplace and the heart and aorta. Illustration of the relation of the thickness of the ventricular wall to the curvature at different points.

We can go further into quantitative verification of this application of the Laplacian law than Woods was able to do. From the results in Table I we can calculate the constant "k" (assuming that the shape of the heart would be the same if it had the normal pressure of 125 mm. Hg in the left ventricle and 25 mm. Hg in the right ventricle). Converting these to the right units (dynes per sq. cm. for P, and cm. for the radii and thickness) and using equation (5) we find that, for the right ventricle, $k = 6.1 \times 10^5$ dynes/sq.cm., and for the left, 4.5×10^5 dynes/sq.cm. Let us take the value of k then as about 5×10^5 dynes/sq.cm. Now, k is the tension per unit thickness of the wall, i.e., the force per unit length (of a "slit") per unit thickness. This is the force that has to be exerted per sq. cm. of cross section of the ventricular wall in order to produce the normal systolic blood pressures. It is interesting to compare this with the values available in the literature for muscle fibers. The new Handbook of Biological Data,[17] Table 281, gives a number of values for striated muscles in man, all of the order of 2×10^6 dynes/sq.cm., which agrees with A. V. Hill's data[9] for striated muscle. Values for heart muscle fibers seem to be lacking, but from Lundin's data[6] for fibers from frog heart ventricles, the force can be estimated as between 1 to 10×10^5 dynes/sq.cm. The values for strips of ventricle are obviously not very reliable, since fibers will be cut. Converted to centimeter-gram-second units the data then give a value of about 5×10^4 dynes/sq.cm., which is understandably lower than Laplace's law demands for the human heart, but might be enough for the smaller cat heart. At any rate, it is evident that the shape and size of the heart is adapted to produce the normal blood pressure with the available contractile properties of cardiac muscle.

So much for the *shape* of the ventricles. The law also reveals a consequence of the *size* of the ventricles that is of much practical importance. As Woods points out, if one heart were twice as big in its linear dimensions as another, the force it must develop in its walls to produce the same systolic pressure would be very much greater. Woods estimated the difference as 8 times, but I think it should be 4 times. The radii of curvature will be twice as great, so that $\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$ will be halved. The tension per unit length of arc, such as APB (Fig. 1), will have to be twice as great to produce the same pressure. If we imagine the heart sliced through at a given horizontal level, the total length of the circumference will be doubled, so that the total force to be developed by the muscle over the cross section of the cut will be 2×2, or 4 times as great (Fig. 3). The wall will also



$P = T(1/R_1 + 1/R_2)$

RADII OF CURVATURE	X2
TENSION. DYNES/CM.	X2
CIRCUMFERENCE'. CM.	X2
FORCE PER FIBRE. DYNES TO PRODUCE THE SAME P.	X4

Fig. 3.—The consequences of dilation of the heart as predicted by the law of Laplace.

have to be thinner; so, if the force of muscle, when it is made thinner by stretching, is proportional to its cross-sectional area, we will have to introduce another factor of twice. (This is how Woods reaches 8 times.) However, this is debatable, since the same number of fibers are operating, even if they are longer and thinner. In any case, it is certain that the dilated heart is at a very great mechanical disadvantage compared to the heart of normal dimensions. Burch[1] has already pointed this out. The eventual failure of Starling's law, (i.e., of the increased force of contraction with increased initial fiber length) when a critical length of fiber is exceeded, is undoubtedly an important factor in heart failure. It may be pointed out that the phenomenon of change of direction in the graph of contractile force versus initial length is not nearly so abrupt for cardiac muscle as it is for striated muscle, where the diagram is so well known. Lundin[6] found, with the fibers of frog ventricle, that the contractile force increased from 6 to 8 times to a maximum at 175 to 200 per cent of the unstretched length. However, in many cases there was no subsequent decrease in tension on further stretch before the fiber broke, and the maximum was quite a "flat" one. The point here is that even though the force is 7 times as great, it needs to be 4 times

as great when the heart is twice as large, and 9 times as great when it is 3 times as large, if the heart is to pump with the same pressure. Detailed data on mammalian heart muscle fibers, as to the increase in contractile force on stretching, seem to be lacking, so that we cannot decide exactly whether "overstretching" or the law of Laplace are most responsible for the point of "decompensation," but clearly both are important.

THE LOAD AND THE EFFICIENCY OF THE HEART

While the increased force of contraction may enable a dilated heart, up to a certain point, to do the same amount of external work in pumping blood, as a heart of normal size, or even more, the "efficiency" will be decreased with the smallest degree of increase in size, even in the "compensated" phase of Starling's law. The energy and oxygen requirements will be increased because of the necessity, when the heart is larger, of maintaining a higher tension in the muscle to produce the same systolic pressure.

So much attention has been paid to the controversial and very difficult details of calculation[7] of the mechanical work of the heart ($\int$ P.dv) that we are liable to forget that by far the major part of the energy requirement of the heart may be not for this but for the maintenance of tension in the heart muscle. We encounter here the old confusion in the mind of one trained in physics when he first encounters problems of physiologic work and fatigue. Work is precisely defined as the product of the force times the distance its point of application is moved. When I push, without success, on the back of my neighbor's car to help him start it, I do no "physical" work, since the point of application of my force does not move at all. Yet, my energy is depleted and my muscles are tired by the attempt. This problem has prompted Starr[8] to suggest a new physiologic definition of work; but to a biophysicist it is unthinkable to alter the precise definition. The terms "static work" and "physiologic work" (Burch[1]) have been suggested.

The resolution of the difficulty is, of course, quite simple. Perhaps the analogy of Fig. 4 helps the understanding. A crane lifting scrap iron by a hook onto a waiting truck does only external work (force $\times$ distance), with, of course, some frictional losses in the engine. When an electromagnetic pickup is used instead of the hook, there is, in addition, the energy cost of maintaining the magnetic force, and this is proportional to the force developed and the time it is maintained. The classical work of Hartree and Hill[9] showed that in muscle the oxygen consumption and heat liberation is proportional to the product of tension developed and the time it is maintained. Thus, the O_2 consumption of the heart depends on the sum of two factors, not merely the mechanical work of the heart ($\int$ P.dv) but also the tension $\times$ time. The mechanical efficiency of the heart is the mechanical work divided by the sum of the two factors, i.e., the term involving tension $\times$ time, plus the term involving work.

Exact formulation is not suitable here, since there are complications. There is probably an interaction term as well, if cardiac muscle, like striated muscle, has a "Fenn effect," i.e., a change in the heat produced according to the change in length. The kinetic energy term is also to be added. However, this will

not affect the main argument here. The efficiency equation is certainly approximately of the form:

$$Eff. = \frac{\int P.dv}{a \int P.dv + b \int T.dt} \qquad (6)$$

"a" would be the reciprocal of the thermodynamic efficiency of the contractile process and "b" could be called an "A. V. Hill coefficient" (since for striated muscle, Hill and his co-workers first measured the relation of heat output to tension × time). In stating this fundamental consideration, I claim no originality. Weiss,[10] in 1913, wrote a most discerning paper on "Le Travail du Coeur" stressing the same point, and Wiggers and Katz[11] considered it in detail.

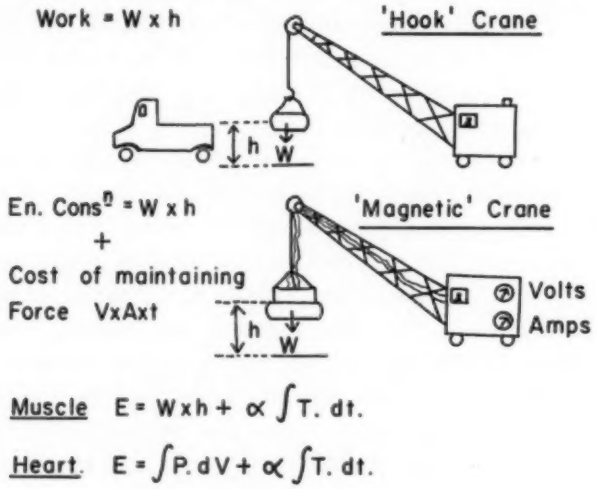


Fig. 4.—Analogy of the electromagnetic crane to explain the energy expenditure of muscle in maintaining tension.

The important question is what is the relative magnitude of these two factors, external work and tension × time, in the energy cost for the heart. I know of no modern quantitative data for the heart muscle that would enable us to calculate this, but there appears to be an answer in the classical papers of Starling and Visscher.[12] Visscher and his co-workers have emphasized their conclusion from similar work, repeated with refined methods of measurement, many times since.[13-15] This is that the total O_2 consumption of the heart, normal or in failure, depends upon the diastolic volume and is relatively independent of the external work the heart is made to do. Sarnoff and associates[16] have recent results with a new "heart lung" preparation that completely confirms this. The law of Laplace thus explains why the diastolic size can alter the energy turnover, by increasing the tension × time required. The fact that the oxygen consumption depends so little upon the work of the heart must mean that of the two factors the *tension × time is much more important than the external work.* This relative importance would also explain why, as has been found repeatedly, the mechanical efficiency of the heart increases markedly when it is made to do more work. The numerator of the fraction that measures efficiency, i.e., mechanical work, increases much more than the denominator, when this is a small item in the total.

It appears, therefore, that we should not spend too much effort on refining our measurements, or on calculating the work of the heart, while neglecting the really important factor, the size and shape of the heart.

THE HEART RATE AND THE LEVEL OF BLOOD PRESSURE

In the clinic and hospital, the heart rate is used as the index of stress upon the heart. We have been inclined to be apologetic and justify this on the grounds that opportunity to measure the actual work of the heart is not easily available. We need not apologize. An increase in heart rate increases the important factor of the total load, i.e., the tension × time, since the duration of systolic contraction decreases very little when the cardiac rate increases. The minor factor, the external work, is of course also increased proportionately, other factors being equal. Thus, the heart rate may well be a better index of total load than the mechanical work of the heart.

An increase in the systolic pressure, such as in hypertension, will of course increase proportionately the tension required in the heart muscle, and so increase the product (tension × time). For the same cardiac output, the mechanical work of the heart will also increase proportionately, so that both factors of the load are increased. If the prolonged hypertension results in dilation of the heart, the load will become very great indeed. It is little wonder that hypertrophy of the ventricular muscle is often seen in hypertension.

Even the loss of elasticity of the aorta with age will impose an increased load on the heart. To accommodate the same stroke volume, the pressure in the aorta will have to be higher, and this means that the ventricular pressure for ejection must rise. Thus, the tension × time factor of the heart increases, as does the oxygen requirement of the heart. In this case, however, the mechanical work ($\int$ P.dv) will not necessarily increase proportionately.

CONCLUSION

The classical laws of physics apply, therefore, as of course they must, to the functioning of the human heart, and emphasize how much concern there should be over evidence of any increase in size of the heart, and how important clinically it is to correct such changes. We should not let our modern preoccupation with details of the calculation of the mechanical work of the heart in pumping blood make us forget that, after all, this is not the chief factor concerned with the total cardiac load. The size of the heart, the heart rate, and the systolic pressure are probably much better indices of cardiac stress than external cardiac work, even where this can be measured. What is needed is more quantitative research, with modern tools of investigation, of the tension × time relations of heart muscle and its thermodynamic cost. Between the production of pressure in the ventricle and the force of contraction of cardiac ventricular fibers lie the simple geometrical mechanics of the heart that may be all-important.

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Original Communications

ELECTROCARDIOGRAPHIC OBSERVATIONS ON TEN SUBJECTS AT SEA LEVEL AND DURING ONE YEAR OF RESIDENCE AT HIGH ALTITUDES

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LIMA, PERU

IT IS well known that at high altitudes chronic anoxic anoxia determines anatomic and physiologic changes in the people living permanently in these places. The classical signs of right ventricular hypertrophy, and those of right bundle branch block, can be found in the electrocardiogram.[1] Positions of the ÂQRS vector in Bayley's 1, 2, 3, and 4 sextants, deep S waves in the left precordial leads, and a tall, late R wave in aVR, all are common findings.[2] The present investigation was undertaken to determine whether similar changes are found in subjects taken from sea level to high altitudes for a period of 1 year.

MATERIAL AND METHODS

Ten normal men between the ages of 18 and 23 years were studied. The investigations were made in Lima, at sea level, and in Morococha at an altitude of 4,540 meters (14,900 feet). Morococha is located a distance of 4 hours by motorcar from Lima, and has a mean barometric pressure of 446 mm. Hg. In the natives living at this altitude the alveolar pO_2 is about 50 mm. Hg, and the arterial blood oxygen saturation, 80 to 81 per cent.

At sea level, an electrocardiogram was taken in basal conditions. At high altitudes, 5 electrocardiographic observations were carried out under the same conditions. In 5 of the subjects these studies were made after 1, 3, 5, 8, and 12 months of residence at high altitudes.* In 5 other subjects the observations were made after 2, 4, 6, 8, and 12 months of residence at high altitudes.

A Sanborn Viso-Cardiette was used in Lima, and a Cambridge Simpli Trol in Morococha. Standard leads, augmented unipolar limb leads, precordial leads, and Lead V_3R were recorded. The model described by Peñaloza and Tranchesi[3] was used in order to calculate ÂP, SÂQRS, and SÂT vectors. In this model the elliptical form of the cylinder, representing the thoracic cage, and the eccentric position of the "electric center" have made it possible to obtain a smaller discrepancy between calculated and real vectors. For some scalar measurements, the projection of the electrocardiograms, with an increase of 10 diameters, was used.

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*One of the subjects deserted after 6 months of residence at high altitudes.

RESULTS

A. *Vectorial Observations.*—The vectorial findings are shown in Table I, and in Figures 1, 2, 3, and 4.

ÂP vector: The frontal projection of P (ÂP) showed only insignificant variations. The mean spatial vector (SÂP) was not calculated because the high thoracic leads were not registered, and it is known, through our own studies, that the zone of null potential of the P electrical field is found, in general, over V_1. However, no substantial changes apparently occurred in the sagittal direction of SÂP.

SÂQRS vector: At sea level the frontal projection of this vector (ÂQRS), with only one exception, occupied the last sextant of Bayley (Fig. 1). After 1 year of residence at high altitudes, most of the cases were located in sextant 5. The right SÂQRS deviation was 70° in Case 10 (Figs. 1 and 2). In 2 other subjects (Cases 2 and 5) the ÂQRS vector shifted from +40° and +30° to −140° and −150°, respectively (Figs. 1 and 3). In only 1 case was no variation of SÂQRS observed (Case 4). In most of the cases there was also a variable degree of backward SÂQRS rotation, which is inferred from the horizontal and sagittal projections of SÂQRS (Table I), as well as from the shifting of the transitional zone toward the left precordial leads.

SÂT vector: Unimportant variations occurred in the frontal projection of this vector (ÂT), while significative deviations on the sagittal plane were observed in some subjects. Cases 3 and 10, in which accentuated backward SÂT rotation was observed, showed negative T waves in the right precordial leads up to V_3 (Figs. 2 and 4). Three cases in which no deviations of SÂT were observed showed T waves which were normal in direction but abnormal in contour (Fig. 3). Finally, in 3 other cases, neither vectorial nor scalar changes of the T wave were observed.

TABLE I. OBSERVATIONS ON ÂP, SÂQRS, AND SÂT VECTORS IN TEN SUBJECTS AT LIMA AND AFTER ONE YEAR OF RESIDENCE IN MOROCOCHA

SUBJECTS	ÂP		SÂQRS						SÂT					
	LIMA	MOROCOCHA	LIMA			MOROCOCHA			LIMA			MOROCOCHA		
			F	H	S	F	H	S	F	H	S	F	H	S
1	+60	+60	+60	−55	+55	+95	−95	+45	+5	+20	+165	+30	+15	+115
2	+65	+65	+40	−30	+60	−140	−145	−50	+40	+15	+105	+40	+15	+105
3	+30	+35	+50	−15	+75	+95	−95	+45	+30	+30	+135	+30	−40	+30
4	+30	+45	+60	−50	+50	+60	−50	+50	+55	+45	+140	+60	+50	+130
5	+60	+60	+30	−45	+30	−150	−150	−60	+25	+25	+125	+35	+25	+120
6	+65	+55	+25	−25	+45	+40	−65	+20	+45	—	—	+50	—	—
7	+75	+75	+75	−30	+80	+90	−90	+65	+60	—	—	+70	—	—
8	+60	+60	+30	−40	+35	+90	−90	+60	+45	+30	+130	+45	+30	+130
9	+65	+65	+60	−60	+45	+75	−80	+30	+5	+50	+165	+45	+30	+120
10	+30	+50	+25	−25	+40	+95	−95	+60	0	+15	±180	+5	−15	+5

F = frontal plane; H = horizontal plane; S = sagittal plane.

B. *Scalar Observations.*—The scalar findings are shown in Tables II and III, and in Figures. 2, 3, and 4.

Heart rate: The heart rate decreased in most cases. In some of them, the heart rate was less than 60 cycles per minute. This change occurred in some cases from the first months. In others it was observed by the fifth or sixth month, after an initial period in which the heart rate was higher than at sea level. In nearly all cases, an important degree of sinus arrhythmia was observed at high altitudes.

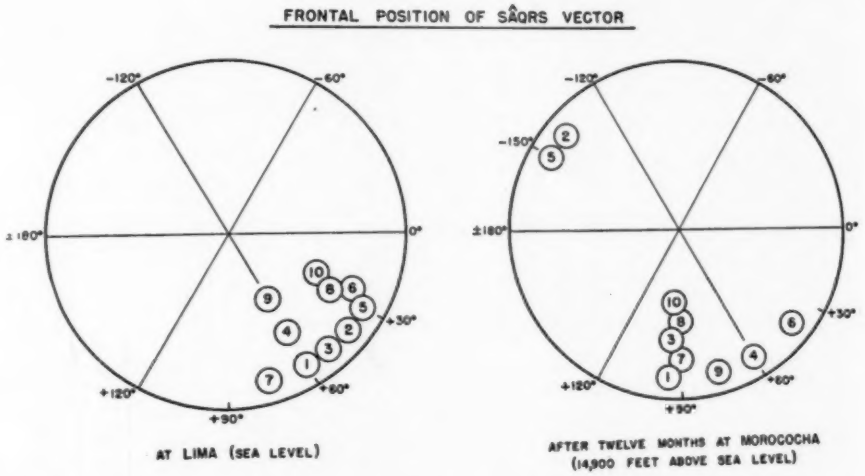

Fig. 1.—The frontal projection of the SÂQRS vector shifts to the right, after 1 year of residence in Morococha. In most cases, SÂQRS shifts from sextant 6 to sextant 5. In Cases 2 and 5, SÂQRS shifts to sextant 3. Only in Case 4 does no deviation occur.

P-R, QRS, and Q-T intervals: Slight changes were observed in P-R, QRS, and Q-T intervals. The variations of P-R and Q-T intervals were proportional to those of the heart rate. The longest Q-T interval, 0.46 sec., was observed in Case 10, after 8 months of residence at high altitudes, when the heart rate was 55 cycles per minute (Table II) and the right precordial leads showed negative, symmetrical, and peaked T waves (Fig. 2). At that period, the difference between the Q-T interval measured and the ideal Q-T interval slightly exceeded the maximal normal value determined from Bazett's formula.

P wave: Throughout our study no significant changes in amplitude, duration, and contour occurred in P waves.

QRS complex: The scalar changes of the QRS complex were proportional to the magnitude of SÂQRS deviation. It can be seen by comparing the values of Table III with the degree of shift in SÂQRS shown in Fig. 1.

The QRS complex frequently increases its negative voltage in Leads I and aVL, and also its positive potential in Leads III and aVF, but the latter does not occur, obviously, when SÂQRS shifts to the third sextant. Changes from qRs or qR types to rS or qrS patterns are frequently observed in Leads I and aVL. Changes from rs or rsr′ types to qR or qRs patterns can be observed in

Leads III and aVF. In Lead aVR the late R wave gradually increases its amplitude and in some cases goes beyond the maximal normal value pointed out by Sokolow[4] (Figs. 2 and 3).

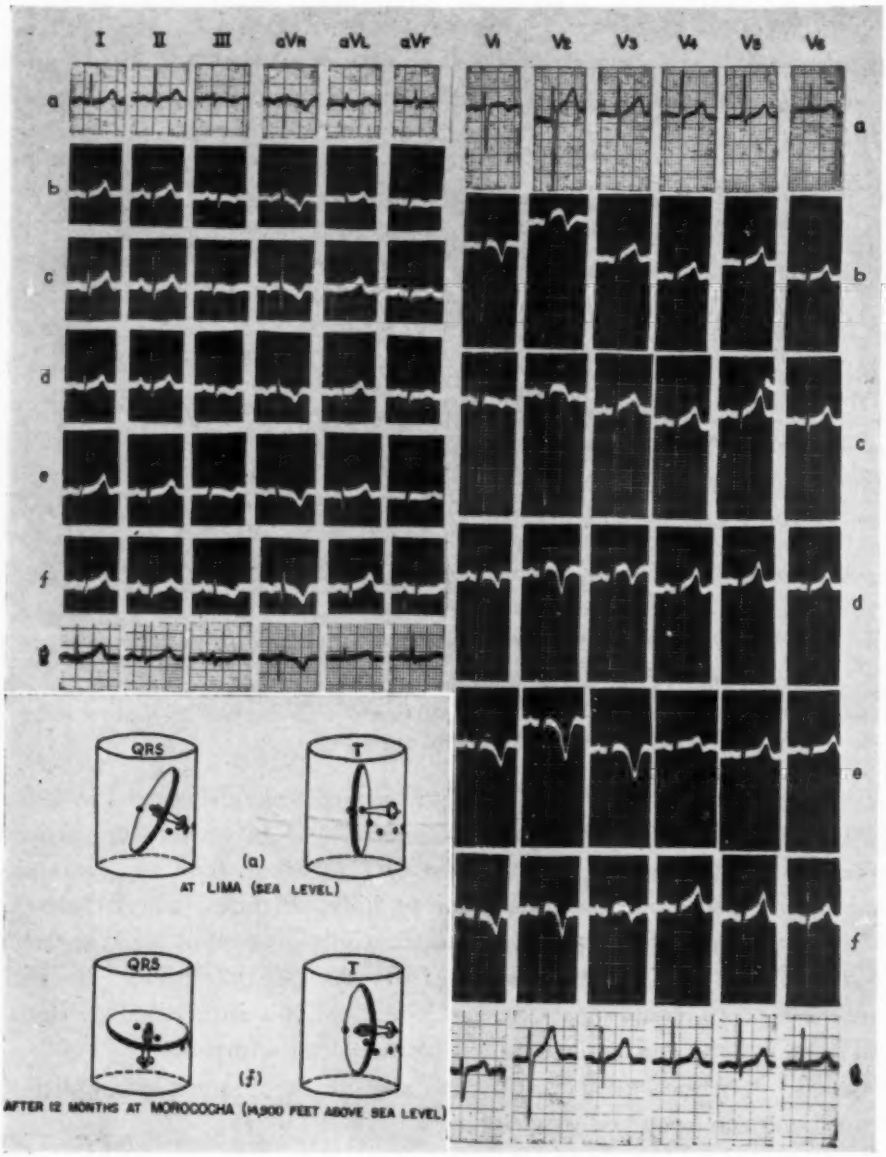

Fig. 2.—Case 10. *a*, Electrocardiogram recorded in Lima. *b*, *c*, *d*, *e*, and *f*, Tracings recorded in Morococha after 2, 4, 6, 8, and 12 months of residence in this place. *g*, Tracing obtained in Lima 1 year later. The SÂQRS shifts to the right and backward, after 1 year of residence at Morococha (*f*). Its frontal projection changes from +25° to +95°. The S wave becomes progressively deeper in Leads I, V_5 and V_6. The late R wave becomes higher in aVR. The QRS transitional complex displaces itself from V_3 to V_4. On coming back to sea level (*g*), these changes disappear completely. SÂT shifts backward, but its frontal projection does not change. In the right precordial leads, the changes of the T wave are progressive up to tracing *e*. In tracing *f* these changes decrease. The RS-T segment in V_2 shows a positive displacement in tracings *b*, *c*, and *d*. All these changes disappeared in the record obtained in Lima (*g*).

In the left precordial leads the S wave becomes progressively deeper, and, also, the R/S index decreases. In Case 2, the QRS complex at sea level is of Rs pattern in V_6, but it changes to an RS, and later on to rS, pattern during the residence at high altitudes (Fig. 3).

In the right precordial leads the R wave and the R/S index do not increase their values, in contrast to that occurring in typical cases of right ventricular hypertrophy. Late R waves in the right precordial leads did not appear in any

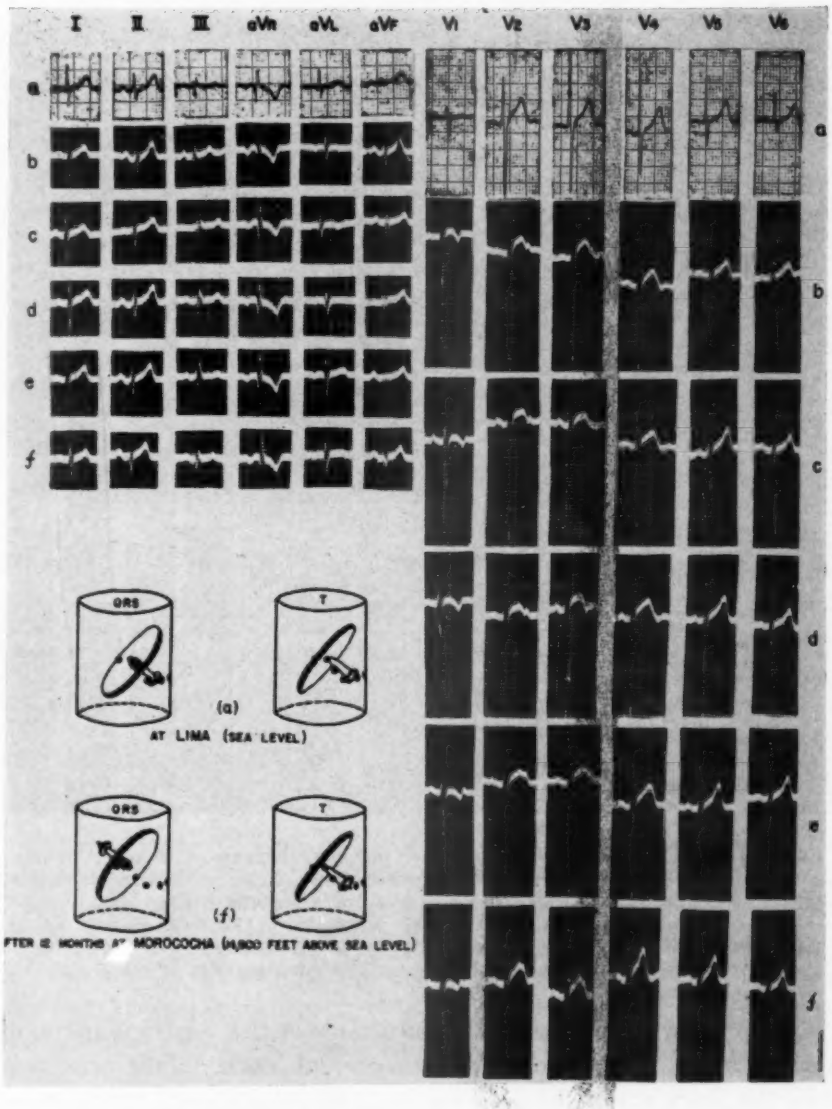

Fig. 3.—Case 2. *a*, Electrocardiogram recorded in Lima. *b*, *c*, *d*, *e*, and *f*, Tracings obtained in Morococha after 1, 3, 5, 8, and 12 months of residence in this place. The SÂQRS shifts from +40° to −140°. Tracing *f* shows predominant S waves in the standard leads, and the late R wave is of great amplitude in aVR. The QRS complex in V_4, V_5, and V_6 gradually becomes negative. SÂT did not vary. In the right precordial leads, the T wave is upright but it is atypical in shape. This abnormality decreases in the last tracing (*f*).

case. In one case a late R wave in V_1 was observed in the tracing recorded at sea level and it remained invariable throughout this study. The time of inscription of the intrinsicoid deflection in precordial leads did not show significative variations.

The index R in V_1 plus S in V_5 gradually increases, and frequently it goes beyond the maximal normal value, 10.5 mm., pointed out by Sokolow.[4] The index $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ progressively decreases. In both indexes the variations are, obviously, due to the increased depth of the S wave in V_5.

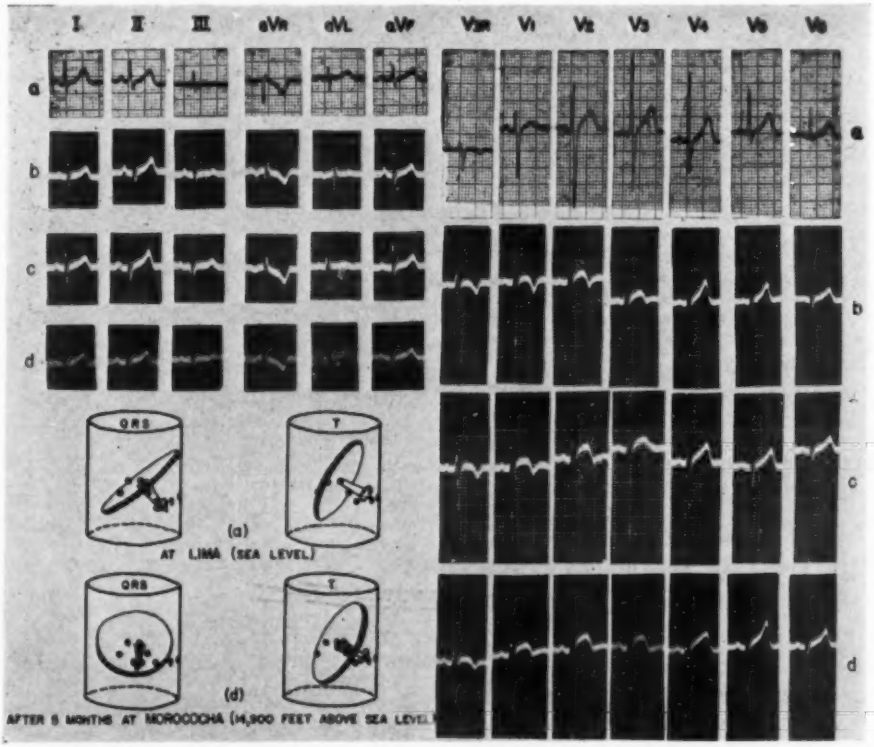

Fig. 4.—Case 3. *a*, **Electrocardiogram recorded in Lima.** *b*, *c*, **and** *d*, **Tracings obtained in Morococha after 1, 3, and 5 months of residence. No further observations were obtainable in this case. The SÂQRS shifts to the right and backward. Its frontal projection shifts from +50° to +95°. The progressive scalar changes in Leads I and aVR and in the left precordial leads can be seen. SÂT shifts backward but its frontal projection does not change. The T wave is negative up to V_3. The displacement of RS-T segment increases up to tracing** *d*, **masking partially the negativity of the T wave.**

RS-T segment and T wave: The variations of the ventricular repolarization process were found only in the right precordial leads. This occurrence is explained by the tendency of the SÂT vector to shift backward, without any change on the frontal plane. The magnitude of the scalar changes was proportional to the magnitude of the backward SÂT deviation.

In some cases in which SÂT remained invariable, no scalar changes of the T wave were observed. In Cases 3 and 10, in which there was an important degree of backward SÂT deviation, those changes were accentuated. In Case 3,

one month after the subject's arrival in high altitudes, the T wave became negative in V_1, V_2 and V_3, and in the same leads the RS-T segment showed a slight elevation with upward convexity (Fig. 4). The latter finding was more accentuated in the following tracing, masking in part the negativity of the T wave. In the fifth month the appearance of the RS-T segment and the T wave is similar to that observed in cases of acute cor pulmonale.[5] Further studies were not carried out on this subject because he deserted.

In Case 10, in the first control carried out at high altitudes, similar changes were observed in the right precordial leads up to V_2 (Fig. 2). In the following tracings the elevation of the RS-T segment decreased and the T wave became negative, symmetrical, and peaked up to V_3, sketching a terminal inversion in V_4. In the last observation, performed after 1 year of residence at high altitudes, these changes decreased in magnitude as well as in extension.

In the remaining cases the changes of the T wave were of less importance. The T wave in the right precordial leads remained upright but it showed an abnormal contour, and a notch appeared in its descending limb (Fig. 3). These changes decreased in the last control, in contrast to those of the QRS complex which were progressive until the last observation.

DISCUSSION

Heart Rate.—A rise in the heart rate in some cases, and a decline in others, was observed during the first months of residence at high altitudes (Table II). Individual differences in the adaptive responses to the influence of a high altitude environment would explain this variable behavior. In almost every subject the heart rate decreased between the fifth and eighth months and an accentuated sinus arrhythmia appeared. Bradycardia and sinus arrhythmia are also common findings in the natives living at high altitudes, and these characteristics have been explained by predominance of the vagal tone.[6]

P-R, QRS and Q-T Intervals.—Only slight variations were observed in P-R, QRS, and Q-T intervals. The P-R and Q-T changes were proportional to those of the heart rate. Only in Case 10 did the measured Q-T interval slightly exceed the maximal value of the ideal Q-T interval, determined from Bazett's formula. This finding coincided with negative, symmetrical, and peaked T waves in the right precordial leads (Fig. 2). The prolonged Q-T interval in this case might be explained by the abnormal way of the ventricular recovery process.

Auricular Activation Process.—After 1 year of residence at high altitudes, the P wave does not show abnormalities. It is interesting to point out that the P wave is also normal in people living permanently at high altitudes. Signs of auricular overloading appear only when the acclimatization to this environment is lost (chronic mountain sickness).[2]

Ventricular Activation Process.—The more important changes in the QRS complex can be summarized as follows: SÂQRS shifts to the right and backward; Leads I and aVL increase their negative potential; Leads III and aVF augment their positive potential; the late R wave in aVR becomes higher; and the S waves in the left precordial leads become deeper. Electrocardiograms with these characteristics have been described either as a result of changes in the heart position or as a consequence of right ventricular hypertrophy.

TABLE II. OBSERVATIONS ON HEART RATE, P-R, QRS AND Q-T INTERVALS IN 10 SUBJECTS AT LIMA AND DURING ONE YEAR OF RESIDENCE IN MOROCOCHA

SUBJECTS*	HEART RATE (BEATS PER MIN.)						P-R INTERVAL (SEC.)						QRS INTERVAL (SEC.)						Q-T INTERVAL (SEC.)**					
	LIMA	MOROCOCHA					LIMA	MOROCOCHA					LIMA	MOROCOCHA					LIMA	MOROCOCHA				
		OBSERVATION NUMBER						OBSERVATION NUMBER						OBSERVATION NUMBER						OBSERVATION NUMBER				
		1	2	3	4	5		1	2	3	4	5		1	2	3	4	5		1	2	3	4	5
1	82	102	100	66	75	68	0.14	0.12	0.12	0.14	0.14	0.14	0.082	0.080	0.081	0.085	0.080	0.081	−0.020	0.000	+0.020	+0.005	+0.020	+0.010
2	83	97	73	70	80	94	0.15	0.15	0.16	0.16	0.16	0.15	0.078	0.077	0.079	0.080	0.079	0.079	+0.010	+0.020	+0.020	0.000	−0.010	+0.010
3	72	88	70	69	—	—	0.14	0.13	0.14	0.14	—	—	0.081	0.078	0.080	0.082	—	—	−0.010	+0.020	0.000	0.000	—	—
4	75	72	70	65	70	69	0.16	0.16	0.16	0.16	0.16	0.16	0.082	0.080	0.083	0.081	0.084	0.080	−0.030	−0.020	−0.010	−0.015	0.000	0.000
5	82	68	63	61	60	71	0.15	0.16	0.17	0.17	0.18	0.16	0.078	0.080	0.081	0.080	0.079	0.080	−0.020	0.000	−0.025	−0.010	+0.010	0.000
6	88	100	75	75	55	88	0.16	0.18	0.20	0.19	0.19	0.16	0.081	0.082	0.078	0.079	0.080	0.082	0.000	+0.020	+0.010	+0.010	−0.010	0.000
7	91	75	75	70	68	83	0.13	0.16	0.16	0.14	0.15	0.13	0.083	0.083	0.081	0.083	0.082	0.082	0.000	+0.010	+0.010	+0.020	+0.030	+0.030
8	66	65	60	64	83	70	0.15	0.15	0.16	0.15	0.15	0.15	0.086	0.087	0.083	0.088	0.084	0.085	−0.015	−0.015	−0.020	−0.005	−0.010	−0.010
9	83	73	65	64	65	56	0.16	0.16	0.17	0.16	0.16	0.17	0.085	0.084	0.087	0.083	0.083	0.084	+0.010	+0.010	−0.015	−0.015	−0.015	−0.010
10	65	75	70	75	55	60	0.16	0.16	0.16	0.16	0.17	0.16	0.078	0.079	0.081	0.080	0.082	0.081	+0.005	−0.010	+0.020	−0.010	+0.050	0.000

*In subjects 1 to 5, inclusive, the observations at Morococha correspond to the following periods of residence: 1, 3, 5, 8, and 12 months. Subjects 6 to 10, inclusive, were studied in Morococha after 2, 4, 6, 8, and 12 months of residence.

**This measurement corresponds to the difference between the Q-T interval measured and the ideal Q-T interval, the latter determined from Bazett's formula: $0.39\sqrt{R - R'} \pm 0.04$.

TABLE III. OBSERVATIONS ON R AND S WAVES IN TEN SUBJECTS AT LIMA AND AFTER ONE YEAR OF RESIDENCE IN MOROCOCHA

SUBJECTS	LATE R WAVE IN aVR		S WAVE IN V_5		S WAVE IN V_6		R/S IN V_5		R/S IN V_6		R/S IN V_1		R/S IN V_2		R IN V_1 + S IN V_5		R/S IN V_5 / R/S IN V_1	
	L	M	L	M	L	M	L	M	L	M	L	M	L	M	L	M	L	M
1	0.60	1.40	1.32	8.03	0.40	2.56	17.57	3.61	53.75	11.01	0.22	0.18	0.46	0.44	4.82	11.71	79.86	20.55
2	4.00	6.33	6.76	14.00	2.86	7.40	2.03	0.78	2.93	0.93	0.63	0.35	0.63	0.50	9.76	18.66	3.22	0.22
3*	1.50	4.03	3.00	11.16	1.00	3.61	4.05	1.74	8.16	3.63	0.41	0.35	0.58	0.35	8.43	16.81	9.87	4.97
4	3.36	4.00	5.50	5.40	2.90	3.50	2.92	1.94	4.37	3.18	0.56	0.43	0.67	0.65	11.16	13.13	5.21	4.51
5	4.00	6.00	6.30	9.66	3.00	6.23	1.71	0.94	2.50	0.98	0.51	0.29	0.34	0.25	9.20	12.52	3.35	3.24
6	2.53	3.10	3.13	7.53	1.10	5.00	4.21	2.69	9.27	2.96	0.22	0.21	0.62	0.59	7.33	12.23	19.13	12.80
7	2.00	2.00	6.10	6.66	3.00	5.20	3.35	1.80	4.60	1.94	——	——	0.50	0.39	——	——	——	——
8	0.30	2.23	2.03	4.50	0.00	2.00	9.19	4.48	12.50	7.16	0.20	0.16	0.35	0.28	4.63	7.50	45.95	28.00
9	0.20	0.10	2.50	6.00	0.20	0.30	7.00	2.05	56.25	28.86	0.24	0.25	0.38	0.21	8.33	11.00	29.16	8.20
10	1.00	3.00	2.05	6.20	0.60	2.40	5.95	2.12	13.33	2.91	0.32	0.32	0.41	0.43	6.55	13.76	18.59	6.62

L = Lima; M = Morococha.

*In this subject the measurement corresponding to Morococha are those obtained after 5 months of residence in this place. No further observations were obtainable.

Clockwise rotation around the long axis of the heart, with backward rotation of the apex, would be the explanation for the aforementioned type of the electrocardiogram. This rotation would be determined by the hyperventilation observed at high altitudes. In Case 10, an electrocardiogram recorded 1 year after the subject's return to sea level (Fig. 2,*g*) was similar to the one taken at sea level at the beginning of this study. This observation apparently would agree with the hypothesis which explains the QRS changes as a result of variations in the cardiac position.

On the other hand, the changes of the QRS complex are similar to those observed in the native residents at high altitudes, even though the scalar and vectorial changes are more accentuated in the latter.[1,2] Electrocardiograms with these characteristics have been described in cases of right ventricular hypertrophy, especially in cases of chronic cor pulmonale.[4,7-11] It is well known that the residents at high altitudes have very large and congestive lungs in which there is an accentuated degree of capillary dilatation but no changes in pulmonary arterioles.[12] In the same subjects, an absolute and relative increase of pulmonary blood volume,[13] and a slight or moderate degree of pulmonary hypertension,[14] as well as right ventricular hypertrophy,[12,15] have been described.* Therefore, it is reasonable to suppose that the QRS changes observed in the subjects of this study have a similar significance. Such changes would be a previous stage to the QRS variations observed in the acclimated residents at high altitudes and would represent, at least partially, an incipient development of right ventricular hypertrophy.

The following observations would favor this last hypothesis: (1) The QRS changes were progressive during 1 year of study, while the hyperventilation decreased. (2) The QRS changes are not rapidly reversible when coming back to sea level, as can be observed in subjects who have lived for a long time at high altitudes and then returned to sea level. (3) The x-ray examination carried out after 1 year of residence at high altitudes showed a slight or moderate enlargement of the transverse diameter and cardiac area, and a slight prominence of the pulmonary artery. (4) In the same subjects the mean systolic pressure in the pulmonary artery and right ventricle is 25 mm. Hg; the total vascular pulmonary resistance is close to 300 dynes/sec./cm.$^{-5}$, and the work of the right ventricle is 10 to 13 joules per minute.[14]

The right ventricular hypertrophy beginning to develop could slowly reverse when the subject returns to sea level. It would explain in Case 10 the electrocardiogram recorded 1 year after the subject's return to sea level (Fig. 2,*g*). The reversion of the right ventricular hypertrophy would be similar to that observed after the surgical treatment in some heart diseases.

In summary, there are enough reasons to suppose that factors relative to positional variations of the heart and right ventricular hypertrophy should be considered in the genesis of the QRS changes observed during 1 year of residence at high altitudes.

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*The mechanism of right ventricular overloading can be outlined as follows: anoxemia→hypervolemia with polycythemia→ increase of the pulmonary blood volume→ pulmonary hypertension→ right ventricular hypertrophy.

Ventricular Repolarization Process.—The T wave became negative in the right precordial leads (Fig. 2) and, frequently, these negative T waves were preceded by upright T waves which were abnormal in contour. In other cases, the abnormal contour of the T wave was the only change (Fig. 3). Finally, in some cases an elevation of the RS-T segment in the right precordial leads was observed in the first months of this study.

These variations are not similar to those occurring during acute anoxia.[16] They are not similar to those determined by respiratory alkalosis.[17]* The changes of the T wave are not correlated with the variations of the heart rate. Finally, they are not proportional to those of incipient right ventricular hypertrophy.

The variations observed in the ventricular repolarization process are similar to those described in cases of acute cor pulmonale.[5] Nevertheless, the subjects of this study were all young and healthy men; they were asymptomatic during their residence at high altitudes and could carry out normal activity.

The T wave and the RS-T segment are of normal configuration in the native residents at high altitudes.[1,2] Nevertheless, when these subjects lose their adaptation to high altitudes (chronic mountain sickness) and an increment of the anoxemia and right ventricular overloading occur, the right precordial leads show characteristics similar to those described in our cases.[2] Therefore, the T and RS-T changes in subjects taken from sea level to high altitudes could be interpreted as evidence of imperfect adaptation to high altitudes, and it is in accord with the observations carried out on other physiologic characteristics of the same subjects.[18]

Right ventricular strain would be the early consequence of the anoxemia, and right ventricular overloading in the new conditions of life. In almost every case these changes decreased or disappeared in the last months of residence at high altitudes, pointing out an improvement in adaptation to this environment.

SUMMARY

1. Ten subjects were taken from Lima, at sea level, to Morococha, at an altitude of 4,540 meters (14,900 feet). The electrocardiographic changes which occurred during 1 year of residence in Morococha were studied.

2. No variations of the auricular activation process were observed.

3. The following observations were made in the ventricular activation process: SÂQRS vector shifted to the right and backward. In Lead aVR the late R wave became higher. In the left precordial leads the S wave became deeper. These were progressive changes of slow development, having an anatomic significance. Two factors were probably responsible for them: variations in the cardiac position, and an incipient development of right ventricular hypertrophy.

4. The following changes were observed in the ventricular repolarization process: SÂT tended to shift backward without variation on the frontal plane. In the right precordial leads the T wave became negative or abnormal in shape.

*Severe hyperventilation was not observed in the subjects of this study. The alveolar pCO_2 and the pH of the blood did not show important variations.[18]

Elevation of the RS-T segment was also observed in the first months. All these changes decreased or disappeared in the last months. A functional significance was attributed to them: they were the early response to the anoxemia and right ventricular overloading.

5. One year of residence at high altitudes was not sufficient time to determine QRS changes as important as those observed in the native residents at these altitudes. One year of residence was also insufficient time, in most cases, for the T wave changes to disappear. The incomplete acclimatization, from the electrocardiographic point of view, after 1 year of residence at high altitudes, was in agreement with what occurred in other physiologic characteristics of the same subjects.

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THE ELECTROCARDIOGRAM OF THE 2-STEP EXERCISE STRESS TEST

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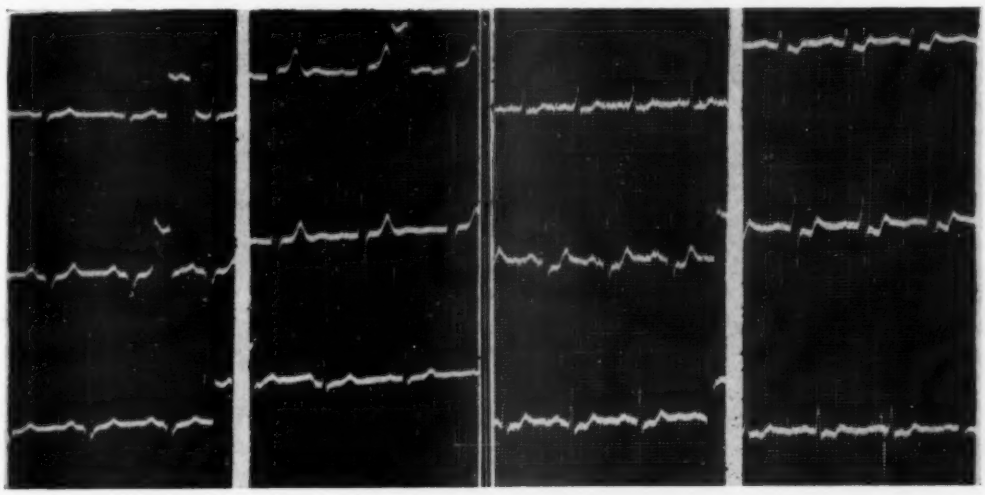
FREQUENTLY the diagnosis of angina, particularly in atypical cases, is difficult. Various forms of stress or effort tests have been studied for many years with a view to producing diagnostic abnormalities in the ECG indicative of inadequate coronary blood flow. Considerable confusion exists with regard to technique and particularly interpretation. The combination of severe exercise and anoxia is known to produce definite and obvious ECG abnormalities in the absence of coronary disease.[1] On the other hand, mild to moderate exertion may have little or no effect on the ECG in individuals with angina. Many investigators have attempted to establish the ideal test, but with little general acceptance. We feel that the individual in whom angina is suspected should first be subjected to approximately the maximal amount of exertion that he is accustomed to, recording the ECG at intervals up to 10 minutes. This, of course, is a most unstandardized method—but one which we have used at times to some advantage (Fig. 1).



A. *B.*

Fig. 1.—Case 1. 39-year-old man. *A*, ECG normal at rest. *B*, Following mild exertion, brisk walk up and down.

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In view of the known effects of posture, exercise, electrolytes, and other physiologic variations on the electrocardiogram,[2] it is of importance that any stress test utilizing the ECG should be standardized as carefully as possible and yet remain practical in the technique of carrying out the test. The modification of the exercise test introduced by Master[3,4] provides a practical and useful standard technique which has met with fairly wide acceptance. There is, however, by no means any such similar acceptance as to the criteria for a positive test or, in fact, agreement as to the diagnostic value of the procedure, although evidence is increasing as to its usefulness in the assessment of angina pectoris.

Fig. 2.—Case 1. Section showing marked intimal thickening. Generalized severe coronary atherosclerosis. Myocardium normal.

Many do not agree with Master's criteria. There is a variation of opinion with regard to S-T segment depression ranging from 0.5 to 2 mm. for an abnormal depression.[5] In view of the unstable nature of the T wave, some disregard T-wave changes in the absence of S-T depression (Fig. 3).

In the interpretation of the test it is important to consider the changes that normally occur as a result of exercise and tachycardia due to exercise (i.e., the immediate tracing). The P wave becomes larger in Leads II and III, and a negative P_3 may become positive. (The P vector becomes more vertical as does the heart.) The auricular T wave becomes more pronounced and it is opposite in polarity to the P wave; also, the auricular wave shortens and, in order to maintain an area equal and opposite to that of P, it also becomes deeper. Furthermore,

the auricular T wave lasts beyond the end of the QRS and therefore can cause the S-T segment to deviate (Fig. 4). In order to avoid errors of this nature, the junction of the P-R with QRS should be used as a reference level; further assistance is provided by extending a sloping P-R interval into the S-T segment, in order to estimate the amount of deviation due to the auricular wave.

There is also a decrease in the ventricular gradient as a result of exercise causing the S-T-T vector to become directed opposite to the mean QRS vector. Moreover, the junction is normally depressed by the tachycardia of exercise resulting in a sloping segment or acute angle of less than 90° between the R wave and S-T segment. These changes disappear quickly as the tachycardia subsides.

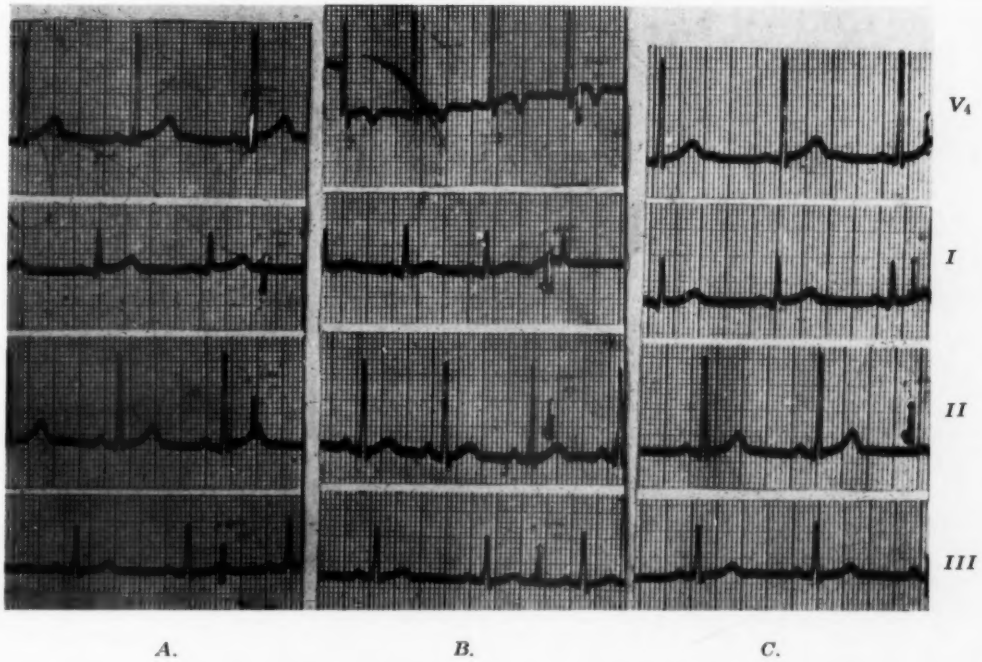


Fig. 3.—Healthy young man, aged 18 years. Two-step exercise test: *A*, before; *B*, immediately after; *C*, 2 minutes after. Immediately following double stress test, T_4 becomes negative associated with cardiac acceleration. Ice water produced similar T_4 inversion again associated with cardiac acceleration. T_4 became negative only with increased heart rate. Normal at 2 minutes after and no segment changes.

When a patient with coronary artery disease performs the test, the S-T-T complex is influenced by these "normal" factors plus the effects of inner layer ischemia, which shortens the duration of recovery, producing a gradient decrease and S-T depression. Another feature of the abnormal S-T segment depression is its flat or sagging nature compared to the rapid rise from S to T in the normal. We have observed that the persistence of the segment depression (or its late occurrence) beyond the immediate, and often the 2-minute, tracing is a feature of the positive test, whereas the depression due to tachycardia (usually sloping up) disappears with the tachycardia.

Since the S-T deviations due to tachycardia and those due to inner layer ischemia have similar direction, the distinction between the two is often difficult.

Examples of obvious S-T abnormalities are seen from time to time in proved cases of severe angina or coronary insufficiency due to other causes (tachycardia, marked fall in blood pressure, anemia, etc.).

In the course of these studies we have observed the effects of exercise in varying degrees on a large number of obvious and proved cases of coronary disease. The degree and type of the S-T change in these cases ought to be taken as an index of what should be regarded as a "positive" response. In other words, one should see in the postexercise tracings changes similar to those which appear in proved cases of coronary insufficiency.

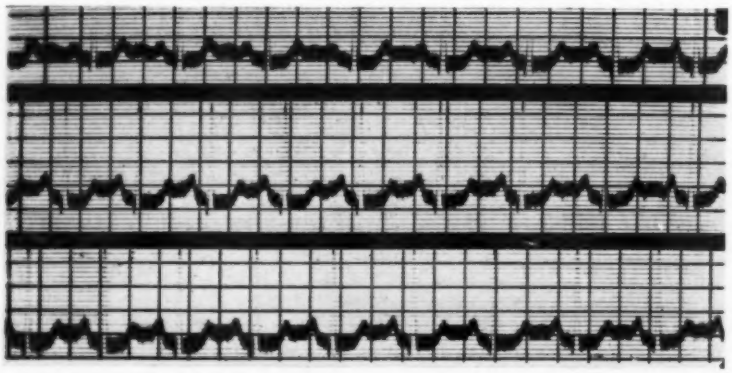


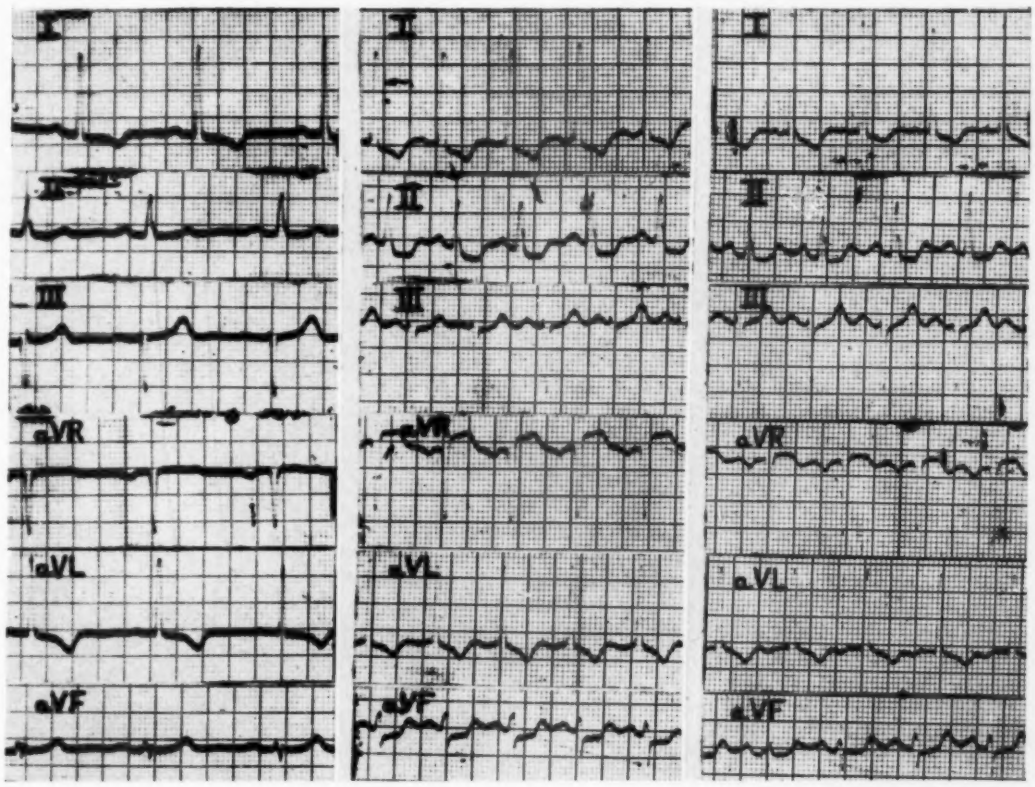
Fig. 4.—Male, aged 36 years. No evidence of heart disease. Sinus tachycardia with false segment depression.

CASE ILLUSTRATIONS

CASE 1.—A very good example of this positive response occurred in a 39-year-old man who was in good health until 8 months before death, when he began to complain of pain in the arms and chest on exertion. An electrocardiogram taken at this time failed to reveal any abnormalities. The pain responded well to nitroglycerin, but it recurred with slight to moderate exertion. Shortly after this, during an admission to Department of Veterans' Affairs Hospital, Westminster, the clinical examination revealed nothing of significance. The blood cholesterol was found to be over 600 mg. per cent. He complained of increasing angina; the electrocardiogram remained normal except following exercise (Fig. 1). Mild exertion produced true S-T segment depression (a full 2-step test was never carried out in this case). Consideration was given to surgical procedures to relieve the angina when the patient suddenly died. Autopsy revealed a very marked grade of atherosclerosis of all major branches of the coronary arteries. The myocardium appeared normal. The heart was not enlarged. Death was considered to be the result of acute coronary occlusion without infarction (Fig. 2).

CASE 2.—This patient, a 77-year-old woman, presented an obvious clinical picture of severe angina pectoris of increasing severity during the previous 2 years. She experienced numerous attacks daily, frequently at rest. She received considerable benefit from nitroglycerin. Electrocardiograms taken during attacks of angina showed an obvious further increase in the segment depression which, following the use of nitroglycerin and on the relief of symptoms, returned to the levels observed before the attack (Fig. 5). This case again illustrates the typical effect of a true S-T depression resulting from a temporary further increase in myocardial anoxia associated with coronary insufficiency. It also illustrates a return of the segments to more normal levels when the degree of myocardial anoxia has been reduced by the use of nitroglycerin, whether this be due to an actual increase in coronary flow or reduction of myocardial oxygen consumption associated with reduced cardiac work.

CASE 3.—In cases of healed myocardial infarction without subsequent angina, one would not expect a positive response unless some degree of coronary insufficiency of the remaining arteries was also present. (There is, of course, no reason for the procedure in such cases of known coronary artery disease.) Although the test should never be done in the presence of acute or recent myocardial infarction, we have had the opportunity to study this in a set of tracings sent to us for interpretation from another center (Fig. 6). The initial tracing in this case revealed the pattern of an acute posterior infarction. The precordial Leads V_1 - V_6 revealed a normal pattern frequently seen in posterior infarction, which may have led to the further investigation. An exercise stress test was carried out in this case shortly after infarction had occurred. This showed definite further segment changes in the postexercise tracing. This case, therefore, clearly illustrates S-T segment changes occurring as the result of myocardial infarction and also the effect of further myocardial anoxia, resulting from exertion in a proved case of coronary artery disease.



A. *B.* *C.*

Fig. 5.—Case 2. Female, aged 77 years. Severe angina. ECG at rest, during classical attack of angina pain, and following nitroglycerin with relief of symptoms. Note segment changes. *A*, Resting, March 28, 1955. *B*, During pain, April 20, 1955. *C*, Following nitroglycerin, April 20, 1955.

CASE 4.—This 41-year-old man complained of chest pain on exertion. He had suffered classical cardiac infarction, confirmed by the electrocardiogram, 6 months prior to this study. During an exercise stress test, carried out at another center, he experienced some shortness of breath. The clinical examination was essentially negative. A single 2-step test was also considered as negative. The effect of a double 2-step stress test certainly raises some question as to whether or not it should be interpreted as a positive test (Fig. 7). This case illustrates the difficulty in assessing the value of the 2-step test. It is an example of obvious coronary disease with a classical posterior infarction 5 months before the stress test was carried out. This man presented a history

very suggestive of angina according to the records. Such a result raises the question of whether or not one should consider this as a negative stress test, which certainly can occur in cases of healed myocardial infarction. It also points out the importance of interpretation with regard to S-T segment depression. The response is considered as doubtful and perhaps it should be considered as negative. In cases such as this, one should rely on the clinical findings and the history rather than the 2-step test. This illustrates that the test by itself can be misleading and of little or no help in certain individuals.

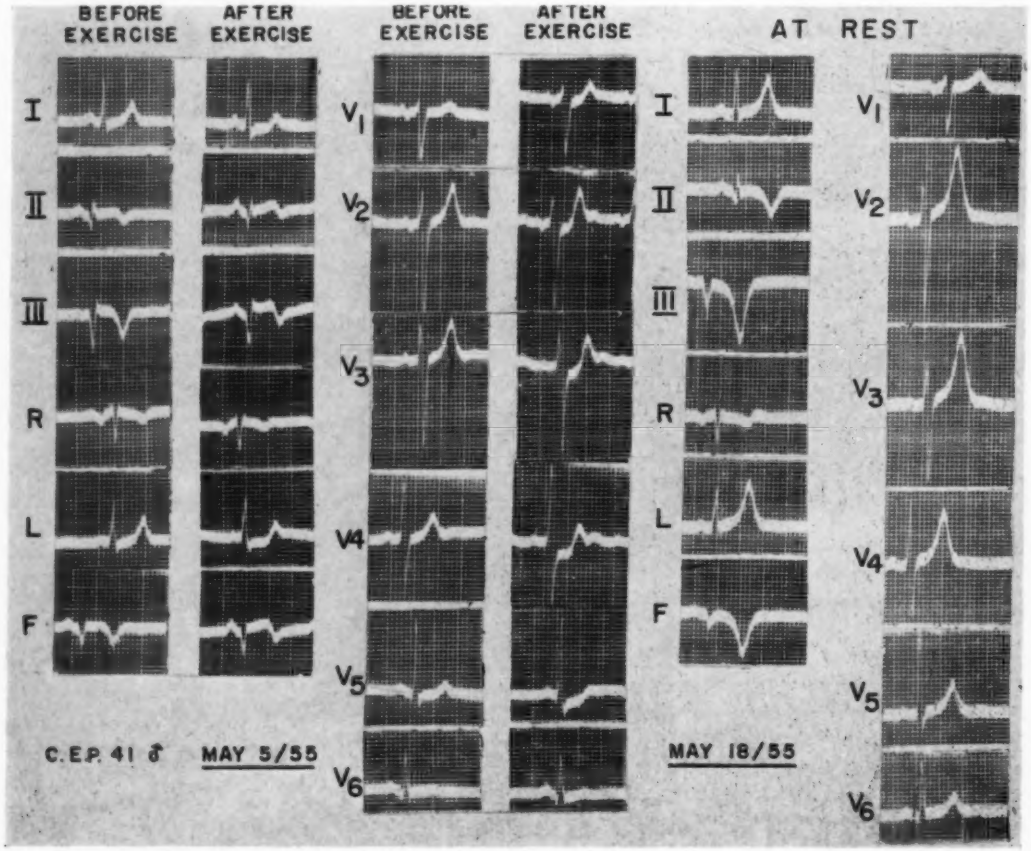


Fig. 6.—Case 3. Male, aged 41 years. The effect of an exercise stress test on the electrocardiogram of acute posterior cardiac infarction. Note segment changes following exercise. Classical posterior pattern 2 weeks later.

It is our opinion that the procedure (or a modification employing less exertion initially in cases of apparent marked decrease in exercise tolerance) is of definite value in many doubtful cases. We feel, however, that more rigid criteria should be employed, while realizing, of course, that such may well result in a greater number of false negative tests. It would seem preferable to occasionally miss the diagnosis than to make a diagnosis of coronary disease when, in fact, none exists. Interpretation of the response to exercise, however, becomes of considerable importance in routine studies required, for example, for selection of aircrew personnel, and in the assessment of cardiovascular status in trained pilots and others in highly responsible occupations, insurance, industry, etc.

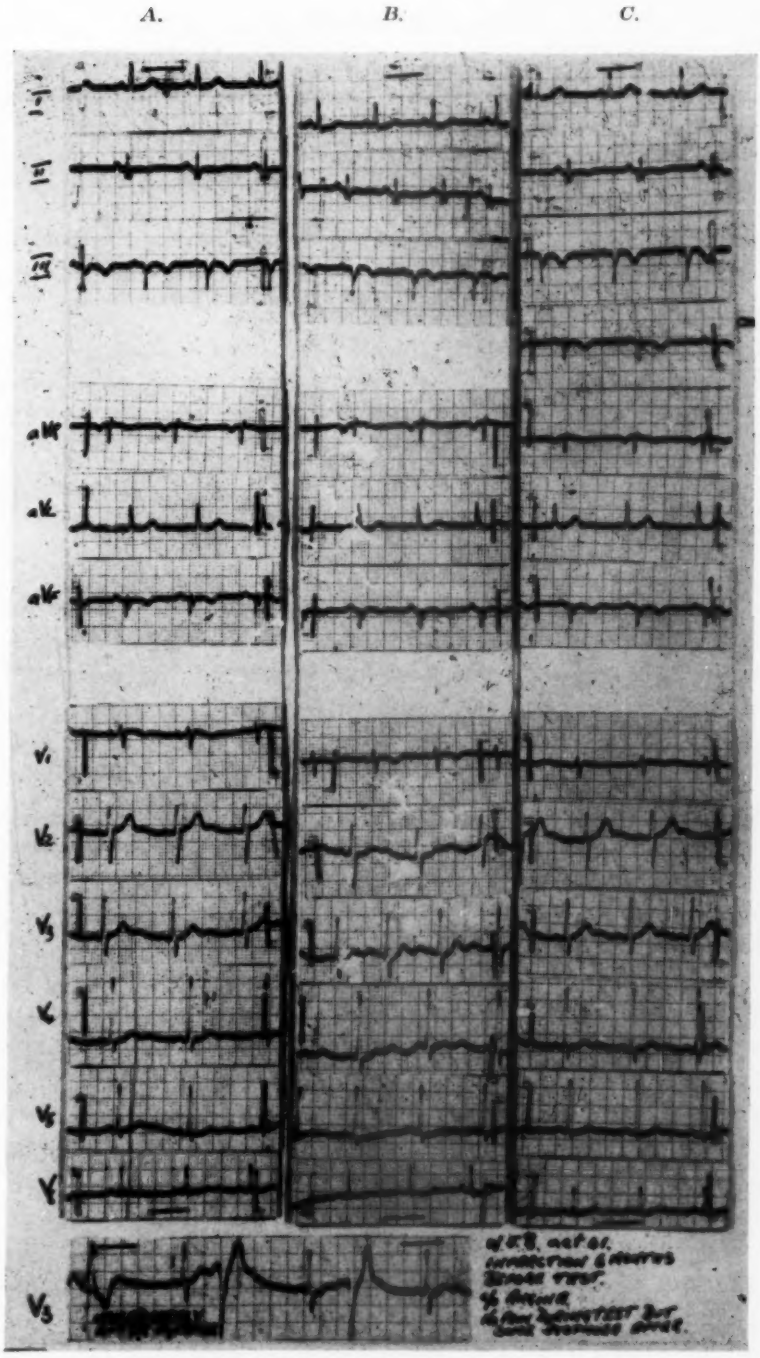


Fig. 7.—Case 4. Male, aged 41 years. Cardiac infarction 6 months prior to stress test. Tracing reveals questionable changes following exercise (see text). Single 2-step test: *A*, resting; *B*, immediately after; *C*, 6 minutes after.

METHODS

In view of the difference of opinion as to what constitutes a positive response in the ECG following exercise, a study of 200 carefully investigated healthy, fit, young men between the ages of 18 and 24 years of age was carried out for comparison with changes observed in proved cases of coronary disease as illustrated above. Although there are a number of well-documented cases of coronary disease in young men, the incidence in a highly selected group should be extremely low. In the group studied, a complete physical examination had been carried out. All showed a normal routine 6-lead electrocardiogram, a 6-foot chest x-ray, psychiatric examination, aptitude tests, etc. Following the extensive selection procedures, all were considered as fit for full flying training in the Royal Canadian Air Force, and consequently represented a highly selected group of healthy, normal young men.

A single and double 2-step test, in accordance with Master's procedure, was carried out in all cases. Simultaneous Leads I, II, III, and V_4 were recorded on a 4-channel Sanborn Poly-Viso recording apparatus.

The exercise stress test was carried out 2 hours after meals, with at least 4 hours intervening between the "single" and "double" 2-step tests. Tracings were taken (simultaneous leads) before, immediately after (within 5 seconds), and at 2 and 6 minutes following exercise, the electrodes remaining in place throughout the procedure.

RESULTS

Since the immediate tracing was obtained within 5 seconds following the stress test, an obvious increase in heart rate was noted in both the single and double procedures (Fig. 8). In this series there was no correlation between positive or "doubtful" results and the heart rate response to exercise. Furthermore in this series, the failure of a heart rate to return to within 10 beats of the resting rate must be considered to be of no significance. There were 6 cases in which the heart rate remained at 10 or more above the resting level at 2 minutes following both the single and double 2-step tests, 15 following the single only, and 26 following the double 2-step test. Thus, there were 47 cases (23.5 per cent) in whom the rate had not returned to within 10 beats of the resting level at 2 minutes following the stress test.

T-Wave Changes.—There were numerous examples of minor alterations in T-wave amplitude. The general trend was to a lowering of T-wave amplitude following exercise and associated with tachycardia. A significant (or obvious) change in T-wave amplitude occurred in 34 instances in the tracing immediately following exercise. A definite lowering of T-wave amplitude occurred in 26 instances in Leads V_4, I or II immediately following exercise, 10 of which became flat or almost flat with a few examples of T-wave notching. There were 5 examples of a marked increase in T-wave amplitude. In 13 instances a negative or diphasic T occurred, 1 revealing a negative T in V_4 in both the single and double tests, 1 a negative T in Leads V_4 and II in the single, and a diphasic T in the double test, and 1 revealing a diphasic T_2 in the tracings taken immediately after exercise. In all 3 instances the T wave had returned to the pre-exercise normal amplitude in the 2-minute tracing.

Variations in the T wave in Lead III immediately following exercise were frequent, including a number of instances in which the direction of the T deflection was reversed. To summarize the T-wave variations, it is apparent that minor to marked T-wave changes are of frequent occurrence in the immediate postexercise tracing in this group of healthy young men.

No significant variations or abnormalities were noted in the P wave, the P-R interval, or the QRS complex in either the single or double exercise stress tests. There were no examples of ventricular extrasystoles or other disturbances of ventricular rhythm in the postexercise tracings.

No significant disturbances of rhythm occurred following either the single or double stress test. In 4 instances, however, auricular arrhythmias were noted in the immediate postexercise tracing, 2 of which revealed only one or two auricular ectopic beats, and 1 revealing a short run of bigeminal auricular rhythm which had disappeared in the 2- and 6-minute tracings. In the fourth example in which the resting P-R interval measured 0.24 second in duration, an upper nodal rhythm appeared in the immediate postexercise tracing of the single test and persisted for at least 6 minutes. In the double test this upper or high nodal rhythm did not appear until the 6-minute tracing. It was felt that the appearance of this rhythm was coincidental, not likely related to exercise and of no clinical significance.

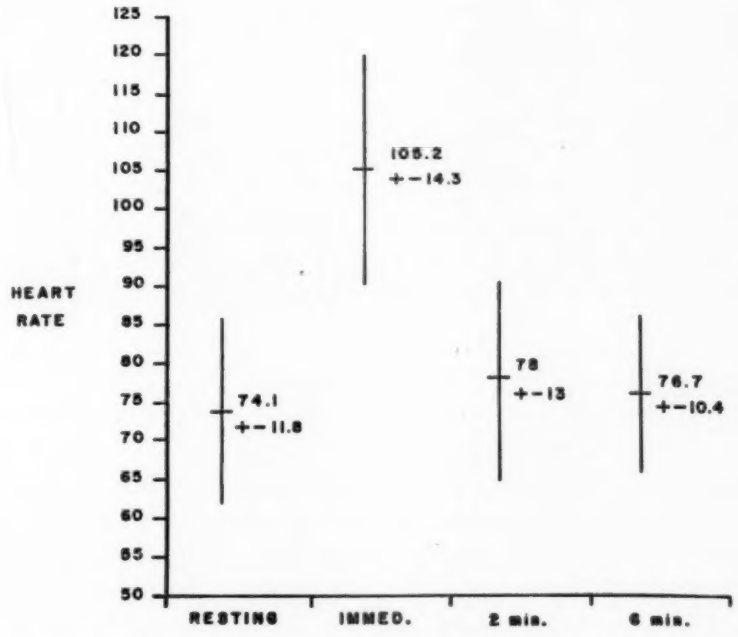
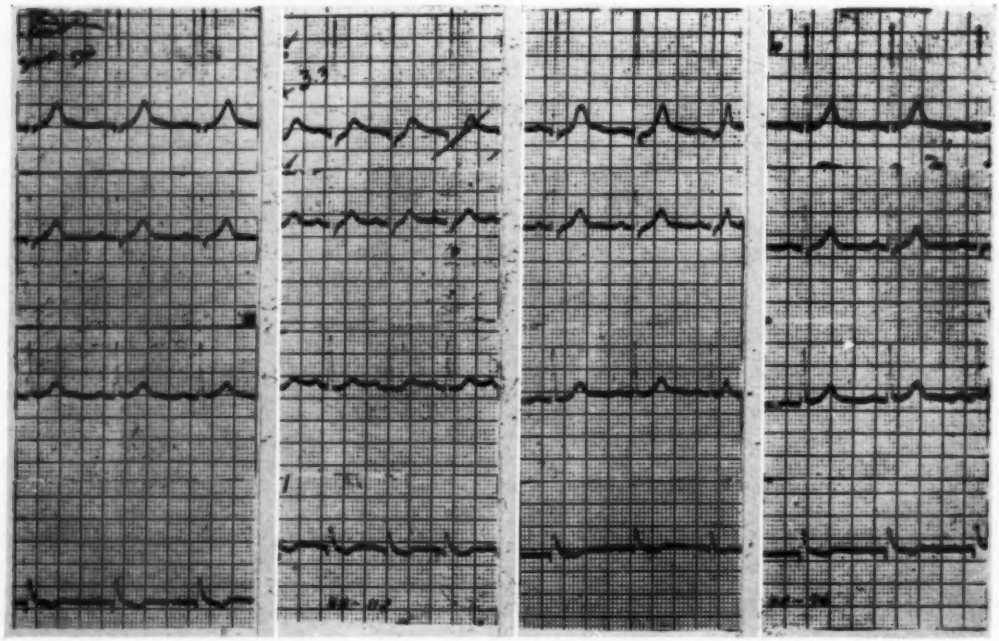


Fig. 8.—Heart rate changes following exercise stress test. Mean and standard deviations of heart rate for 200 healthy males, resting, immediately after, and 2 and 6 minutes after a double Master's 2-step test.

RS-T Segments.—There were numerous examples of apparent S-T segment depression of 0.5 mm. or slightly beyond this (Fig. 9). In the tracing immediately after exercise many were associated with a depressed J junction and upward sloping segments. The questionable depression had returned to normal in the 2-minute tracing, coincident with a reduction of the heart rate (to normal). Extension of the sloping auricular T-wave segment through the QRS into the S-T segment was of considerable help in studying the immediate postexercise

tracing. In leads with an absent S, assessment of the postexercise tracing was simplified since the confusion of a depressed J junction did not occur. The sloping segment, often confused as being depressed in this group, was normal in the 2-minute tracing, supporting the view that a true depression subtends an angle of 90° or more with the vertical and persists (or may appear later) beyond the immediate tracing.



A. *B.* *C.* *D.*

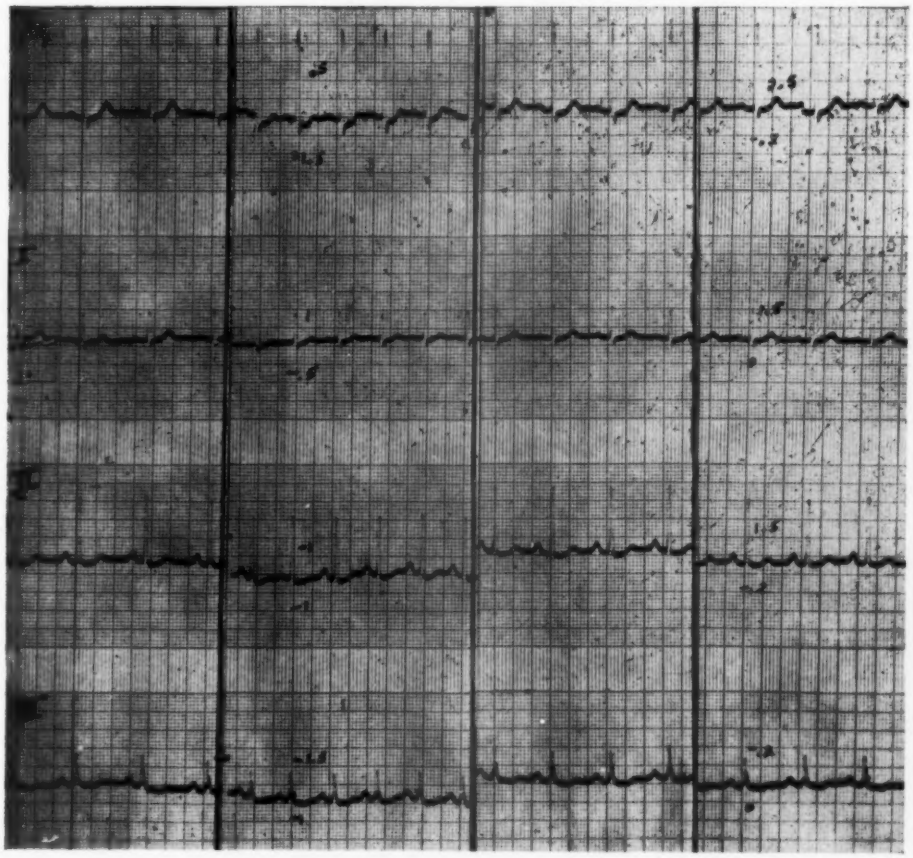
Fig. 9.—Healthy aircrew trainee, aged 20 years. Leads V_4, I, II, and III. Note upward sloping segment depression in immediate tracing; normal at 2 minutes. *A*, resting; *B*, immediately; *C*, 2 minutes; *D*, 6 minutes after test.

In 17 instances it was difficult to assess accurately the degree of segment depression. In these cases a depression of 0.5 or more was present in the immediate postexercise tracing of the double test, and in many of these instances with the single test. The segment had returned to normal by the 2-minute tracing and it was our opinion that all should be interpreted as negative responses, when one considers the false depression associated with tachycardia, auricular T waves, depressed J junction, and upward sloping segments.

In 4 instances a very questionable depression occurred which persisted beyond the immediate postexercise tracing. In 1, Lead III, following the double-step test, revealed a segment depression of 1 mm. The depression in Lead II of this case was considered not to be a "true" segment depression. A follow-up study 2 years later revealed a perfectly fit young pilot. The stress test showed similar findings, but was unquestionably negative on this examination. In 1, the segment in V_4 was depressed 1 mm. in both the single and double test, but showed a slight upward slope and was almost at the pre-exercise level at 2 minutes. In the third case of this group, V_4 revealed an upward sloping depressed segment of 1.5 mm.

in the immediate postexercise tracing of both the single and double tests. Lead II of this case also showed a depression of 1 mm. Some depression was present at the 2-minute tracing and normal at 6 minutes. One tracing (Fig. 10) revealed a significant depression similar to that seen in proved cases of coronary insufficiency.

These 4 examples are considered separately since they represent the only questionably positive cases in the series. Only 1 (Fig. 10) showed a segment depression not due to tachycardia, auricular T waves, depressed J junction, etc., and quite similar to the type of segment depression observed in proved examples of coronary insufficiency. In a follow-up study 2½ years later this man was



A. *B.* *C.* *D.*

Fig. 10—Healthy aircrew trainee. Note segment depression V_4 persisting at 2 minutes. This is considered to be the only positive case in the series. *A*, resting; *B*, immediately; *C*, 2 minutes; *D*, 6 minutes.

found to be perfectly fit and completely normal following a complete cardiovascular assessment. The single 2-step test was negative on this examination; the double step test again revealed a "flat" segment depression of 0.5 to 1 mm. The remaining 3 cases, in spite of the obvious depression, revealed other features which would place them in the doubtful or questionable category and which we would consider as likely negative.

DISCUSSION

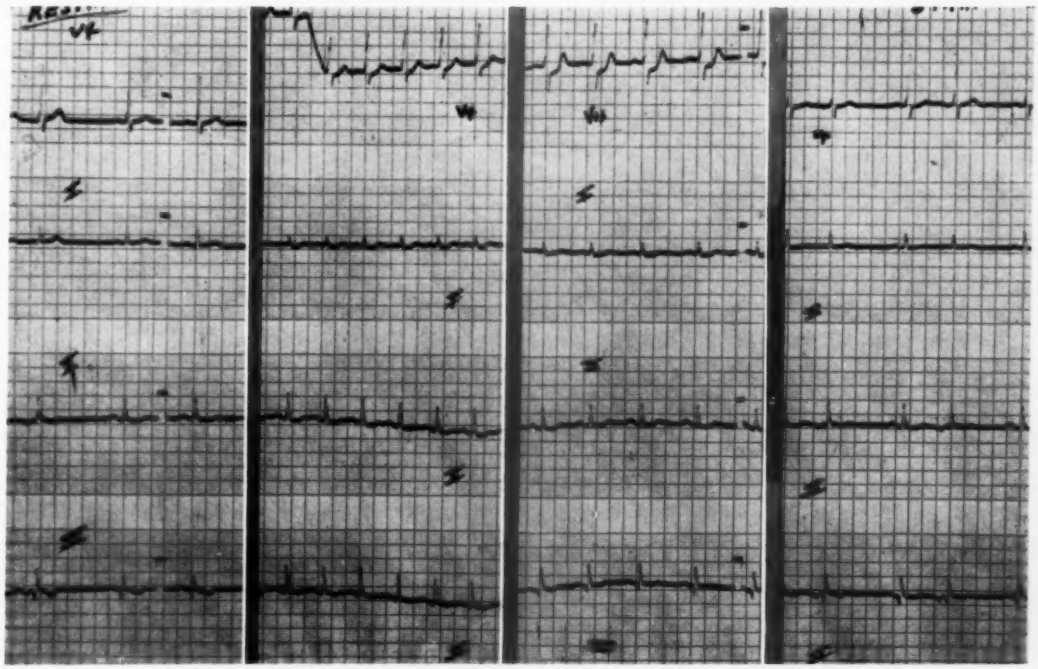
A number of case reports have been presented to illustrate the effect of exercise on the RS-T segment in proved examples of coronary artery disease. A true depression presents a number of specific characteristics. The depression is of a "flat" character subtending an angle of 90° or more with the vertical and greater than 0.5 mm. below the P-R segment.[6] From our experience, the depression of the segment persists beyond the immediate tracing to the 2- or 6-minute tracing, or even longer, or it may not appear until the 2-minute tracing. In some instances a definite depression of the segment occurs and, superimposed on this, the effect of tachycardia and an upward slope may be present. Usually the 2-minute or later tracings will reveal a "flat" depression in "positive" tests. In this study of 200 highly selected fit and healthy young men, a number of stress tests fell into the questionable group. If such findings had occurred in older individuals, particularly ones in whom angina pectoris was in question, it is possible they would have been considered by many as positive tests. Variations in T-wave amplitude and direction were frequent. "False" segment depressions were common. However, viewed in the light of stricter criteria, we feel that only 1 of the 200 should be considered as a positive test. It is apparent, therefore, that misleading changes following the exercise stress test are of frequent occurrence in the normal.

Considering the variations that may occur in T-wave amplitude and direction, segment depression associated with tachycardia, T-wave changes associated with cardiac rotation, effects of meals, temperature, etc., it would appear that only a "true" segment depression should be accepted as indicative of myocardial ischemia following an exercise stress test. A segment depression of 1 mm., providing it is of the "flat" type and persists (or first appears) beyond the immediate tracing, should be regarded as a positive response. Depressions of 0.5 to 1 mm. which fall into this category should be considered as questionable and likely positive, providing they are unquestionably of the flat type. Furthermore, depressions in the immediate tracing of 1 mm. or more which also present an upward slope (probably associated with tachycardia) and which in the 2-minute or later tracing have lost the upward slope and present as a "flat" depression should be considered as positive responses. If one accepts only those cases which show a true and significant segment depression as positive responses, it is possible that some cases of angina will be regarded as normal. On the other hand, if more liberal criteria are accepted, a diagnosis of angina may be made in many instances where, in fact, none exists. In the questionable cases (and the procedure is only for use in doubtful cases with normal ECG) an exercise stress test is really of value only if it is positive. A negative test does not rule out coronary disease, although if it remains negative following strenuous exercise, we believe it to be supportive evidence against a diagnosis of angina. If after a double 2-step test, in which the clinical evidence is equivocal, the response is negative, it is in the best interests of the patient to consider that he does not suffer from angina.

Although it is felt that some cases of true angina will be missed by the adoption of such a policy, much more harm will be done by accepting a diagnosis of

angina, particularly when the clinical evidence is very questionable. On the other hand, if the test is definitely positive, then we are aided greatly in arriving at the diagnosis.

When routine exercise stress tests are carried out for any purpose, great care must be taken in the interpretation of the tracings. Very strict criteria should be followed and only true segment depressions accepted as positive responses. In this series, only 1 in 200 apparently fit, healthy young men was considered to be a positive response. Although the significance of this finding is not clear, it is reasonable to assume that 1 in 200 even in this age group may have appreciable coronary narrowing or other coronary abnormality to account for the changes observed.



A. *B.* *C.* *D.*

Fig. 11.—Male, aged 54 years. Chief complaint was headache on exertion, followed by vague chest discomfort. From history and clinical findings, this patient was considered as psychoneurotic. Single 2-step test is positive. *A*, resting; *B*, immediately; *C*, 2 minutes; *D*, 6 minutes after test.

With regard to the exercise or stress to which the patient should be subjected, we have adopted for routine use the technique described by Master.[3] Many feel that much more strenuous exercise should be carried out.[7] Wood has reported that only 5 per cent of electrocardiograms remain normal during or immediately after an attack of true angina or after sufficient exercise to cause breathlessness and fatigue in patients with ischemic heart disease. In many proved cases of angina we have found the test to be positive on mild exertion, ordinary walking (Fig. 1). In doubtful cases in which it is felt the patient should be exercised, it is reasonable to subject the individual to exertion similar to that which in the past has produced his symptoms and then to record the electrocardiogram.

Such a procedure is certainly safe. If the test is negative following this, then the single and later double 2-step stress test might be carried out. We have used this procedure to advantage in doubtful cases (Fig. 11).

The exercise stress test is of value in doubtful clinical problems if the response to exercise resembles the findings obtained in proved cases of ischemic heart disease subjected to exertional stress. The degree of stress to which the individual should be subjected depends on the case being investigated. Graded exertion up to a double 2-step test appears to be a safe procedure. Ideally, the procedure is to be used as an adjunct to the investigation of doubtful cases of ischemic heart disease. When it is used as a routine procedure in examination for cardiovascular fitness (for military, aviation, or other occupational purposes), only obviously positive responses in which there is no question of a "true" and important segment depression should be regarded as of any significance.

CONCLUSIONS

1. The exercise stress test is of diagnostic value in many selected cases suspected of ischemic heart disease.
2. In proved cases of angina a "true" depression of the RS-T segment usually occurs with the attack and also following exertion.
3. A graded exposure to exercise depending on the case being investigated up to the double 2-step test has been found to be of value.
4. In a study of 200 normal young men only 1 showed a significant segment depression and was considered to be a positive response.
5. False segment depressions in the tracing made immediately following exercise and variations in the T wave in the normal were frequent.
6. The only valid change in the postexercise tracing that constitutes a positive response is a "flat" depression of the RS-T segment as compared to the P-R segment which subtends to an angle of 90° or more with the vertical and persists to at least the 2-minute tracing. A depression with these characteristics of 1 mm. constitutes, we feel, an unquestionably positive response. Depressions ranging from 0.5 to 1 mm., providing they possess the true "flat" characteristics, are considered questionable and likely positive. A positive test closely resembles the RS-T depression pattern seen in proved cases of angina.

The assistance of Dr. T. Jory and Dr. R. Groshaw, who carried out the studies in the normal cases, and to the Medical Selection Unit, Royal Canadian Air Force Station, Crumlin, Ontaria, is gratefully acknowledged. Our appreciation also is expressed to Mr. Gordon Steward and Miss M. Gossman of the technical staff.

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SOME INTERRELATIONS BETWEEN VENTILATION AND CIRCULATION

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INTRODUCTION

ALTHOUGH the importance of ventilation upon circulation is generally recognized, particularly with respect to mechanical devices for artificial respiration, there have been few studies published dealing with the quantitative aspects of this problem during spontaneous respiration. All too often these relationships are neglected in the analysis of either ventilatory or circulatory mechanics. For example, the circulatory effects of bronchodilators in the treatment of bronchospastic disease might play an important role in the relief of bronchospasm.

Therefore, an analysis of some of the factors playing a role in the interrelationship between ventilation and circulation has been attempted. The hypoxic and hypercapnic influences upon pulmonary hemodynamics will not be considered in the present study.

The material presented includes evidence from our own studies and from other publications as well in order to stress the points which have been considered essential.

VENTILATORY EFFECTS UPON CIRCULATION

A. *Respiratory Variations in Stroke Volume and Vascular Resistance.*—The ventilatory activity of the thorax can be considered as an additional circulatory pump. The greater negativity of the intrathoracic pressure during inspiration enhances venous return, thereby increasing the stroke volume of the right ventricle. This leads to a larger filling of the lesser circulation, followed by an increased filling of the left heart and a rise in left ventricular stroke volume. During periods of decreased negativity (expiration and positive pressure breathing) the reverse occurs. The efficiency of this pump action, however, depends upon a number of other factors governing cardiac inflow and outflow. For instance, inflow depends not only upon the gradient between extrathoracic and intrathoracic pressures but also on the amount of venous collapse occurring at the

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points at which the great veins enter the thorax. Outflow, on the other hand, is a function of the contractile force of the myocardium in relation to the diastolic filling and the capacity of the vascular bed. In addition, many of these factors are time dependent.

Dornhorst[1] has shown that resistance and capacity of the lesser circulation introduces a phase lag between the response of the right and left ventricle. At fast respiratory rate there is a decrease in stroke volume variations, and an increase in phase lag, leading to a fall in left ventricular stroke volume during the inspiratory rise in right ventricular stroke volume. He also suggested that the enhancement of the stroke volume modulations in the upright position might be due to a steeper slope of the effective filling pressure-output curve at low filling pressures.

The ventilatory changes of the lung affect not only the stroke volume but also the resistance and capacity of the pulmonary vascular bed. During inflation of the lung, an initial straightening of the vascular bed occurs, and the greater negativity of intrathoracic pressure during inspiration tends to dilate the vessels. This leads to an initial decrease of vascular resistance. The effect of intrapleural pressures upon dilation of the vascular bed, however, is only small.[2] Therefore, as inflation of the lung continues, the vasculature is stretched and the resistance to blood flow increases. This increase in resistance outweighs, by far, the initial decrease.[3] In dogs, this has been confirmed both in closed and open chest preparations (positive and negative pressure inflations).[4] The degree of inflation at which vascular resistance starts to rise depends primarily upon the capacity of the vascular bed. If the vascular bed is reduced, for instance in severe chronic pulmonary emphysema, vascular resistance must rise at much lower lung volumes than in the normal subject.

In a distensible system, such as the pulmonary vasculature, the caliber of the vessels depends upon the transmural pressure. At low transmural pressures, the vessel caliber is minimal and some of the vessels are probably completely closed off. As the transmural pressure rises, the vessel caliber increases and resistance to flow decreases in proportion to the fourth power of the radius. The ease with which the caliber increases is determined by the pressure-volume characteristics of the vessel. Toward the upper part of the pressure-volume curve, the vasculature behaves more and more as a rigid system. Therefore, pulmonary vascular resistance decreases as either pulmonary arterial pressure or left atrial pressure increases until a plateau is reached where further pressure changes are without effect upon pulmonary vascular resistance.[5] The pressure level at which this plateau occurs is obviously determined by the pressure-volume characteristics of the pulmonary vasculature, i.e., the capacity of the vascular bed and the physical characteristics of its wall.

B. *Transmission of Intrathoracic Pressures.*—Intrathoracic pressure changes are transmitted to all elastic intrathoracic structures and can be measured by the introduction of a pressure-sensitive device if these structures are hollow (Fig. 1). The recorded pressure will deviate from the actual intrathoracic pressure

by a fixed or variable amount.* This deviation depends upon the pressure-volume characteristics of the walls and the surrounding structures of that particular hollow organ (for example, esophagus or intrathoracic blood vessel) and the existing connections between the organ and the extrathoracic space. An additional, but determinable, pressure difference may be introduced by the pressure-volume characteristics of the measuring device. The difference between the intrapleural and intravascular measurements of respiratory pressure variations for a given cardiac output then permits conclusions concerning the physical charac-

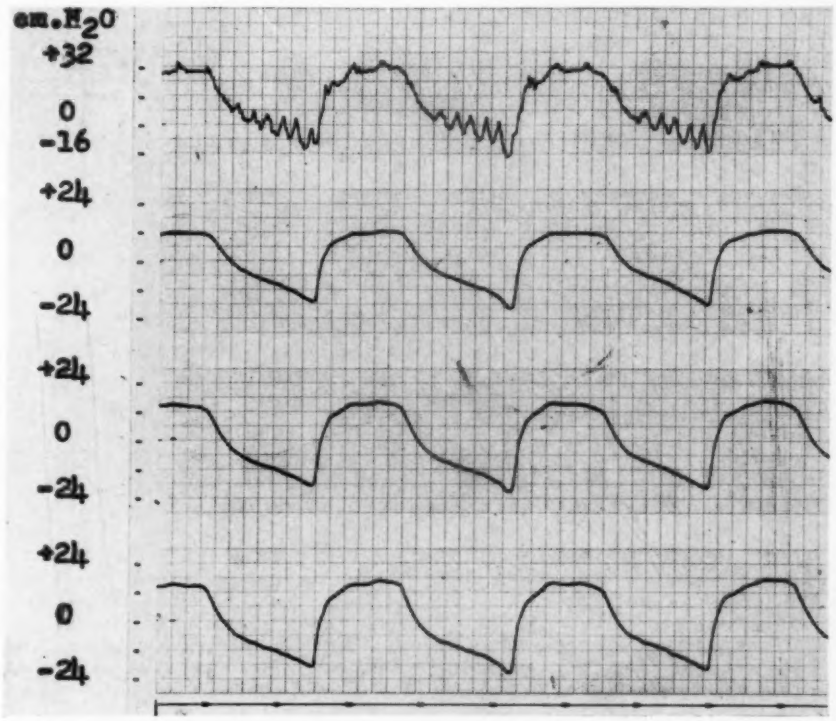


Fig. 1.—Change in right auricular hemodynamics with change in intrathoracic pressure. Note the equal pressure fluctuations at two different sites in the intrapleural space and the esophagus. In contrast, the atrial pressure tracing shows larger fluctuations and enhancement of atrial systole during inspiration and depression during expiration. Tracing from top to bottom: right auricular pressure, esophageal pressure, posterior mediastinal pressure (intrapleural), anterolateral intrapleural pressure.

*The pressure difference between the intrapleural space and an intrathoracic structure remains constant only if the anatomic relationships and/or the tone of the latter are stable. A change in either of those two factors introduces a change in the pressure relationship between the two sites. Volume changes of a hollow intrathoracic organ, variability of the connection between an intrathoracic and an extrathoracic structure, and finally a change in body position may produce an alteration in the pressure relationship purely on an anatomic basis. Though such changes may occur quite suddenly, they are usually not rhythmic if they are not related to either cardiac or respiratory activity. Therefore, they rarely interfere with the interpretation of data in regard to ventilatory mechanics or pulmonary hemodynamics. Sudden changes in tone may occur quite frequently, particularly in the esophagus. During a spasm, the pressure relation between the spastic structure and the intrapleural space is extremely variable, making a proper interpretation of respiratory and circulatory events from such tracings impossible. Fortunately, such events are recognized with relative ease in a proper tracing, if one bears in mind these various possibilities.

teristics of that particular hollow organ, if one assumes that the properties of the surrounding tissue remain unaltered. This would be of particular interest in the study of changes in the pulmonary vasculature.

The total respiratory intrathoracic pressure difference between inspiration and expiration is primarily dependent upon the elastic and flow resistive properties of the lung. Only in bronchospastic disease do the pressures due to the flow resistive properties become proportionally more important than the pressures due to the elastic properties.[6]

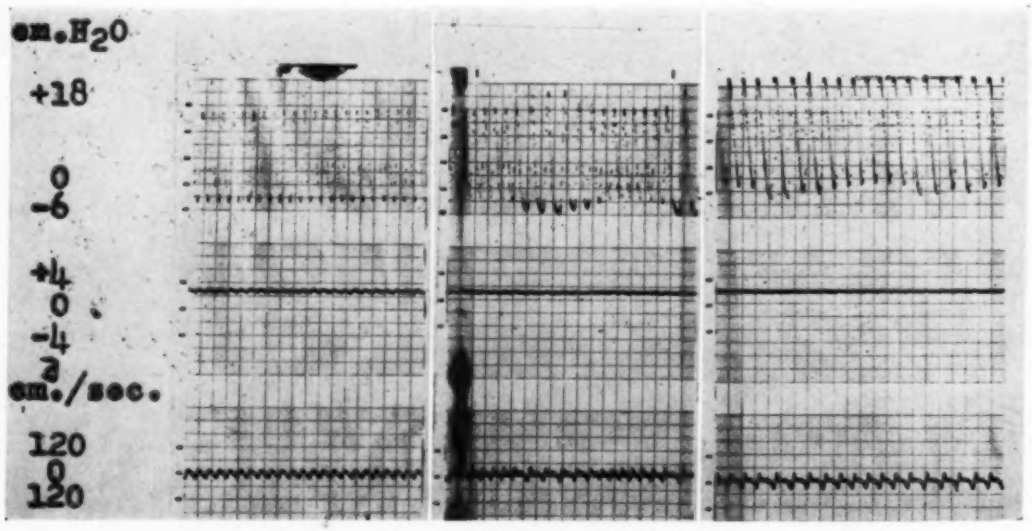
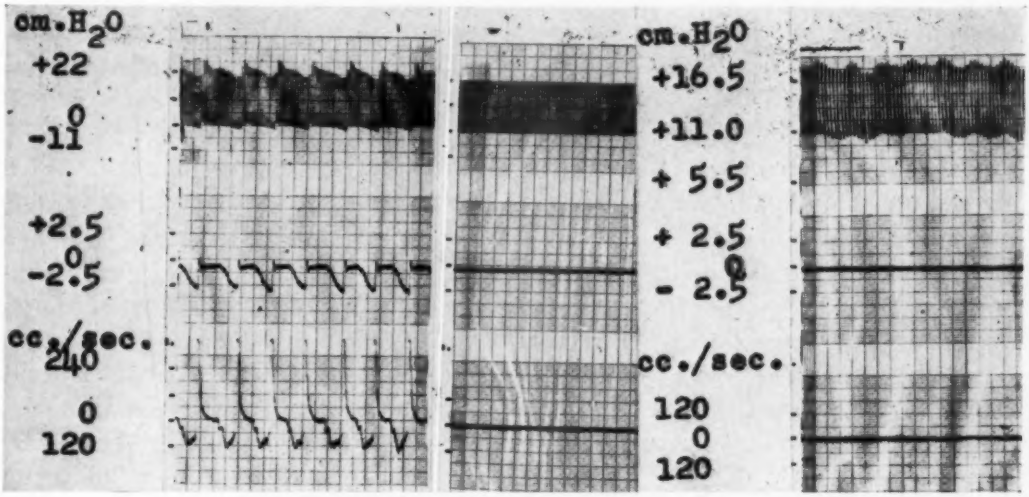


Fig. 2*A*.—Appearance of "respiratory" pressure variations in the absence of intrathoracic pressure changes during diffusion respiration in a male dog weighing 25 pounds. Sinus arrhythmia is also associated with changes in pulse pressure. Tracing from top to bottom: right ventricular pressure, right intrapleural pressure, airflow. *A*, 2-minute $\bar{p}$ induction of diffusion respiration by 50 mg. succinylcholine. *B*, 75-minute $\bar{p}$ induction of diffusion respiration. (Note arrhythmia and "respiratory" pressure variations in right ventricular tracing.) *C*, 80-minute $\bar{p}$ induction of diffusion respiration. (Note that sinus arrhythmia begins to disappear.)

In a series of 22 patients with heart disease[7] in which both ventilatory mechanics and pulmonary hemodynamics were studied, the difference between inspiratory and expiratory pressures in various segments of the vasculature were found to be quite different. In general, right atrial pressure variations were either equal or less than intrapleural pressure variations. Because of the partially open extrathoracic connections via the vena cava, the smaller pressure changes would be expected. The respirtory pressure variations increased toward the left heart, reaching a maximum in the pulmonary capillaries. In the left heart, they were somewhat less than in the pulmonary capillaries but considerably greater than in the right heart. Unfortunately, no corresponding data for normal subjects are yet available, but the same phenomenon was found in dogs.[8] This variable transmission of intrathoracic pressure changes illustrates the difference in the physical characteristics of the various segments of the vasculature. The difference in pressure transmission is not necessarily due only to differences

in capacity and/or wall characteristics, but possibly also to active vasomotion. Evidence for the latter is found in a reversal or a sudden disproportion of the relation in pressure variations between pulmonary and peripheral arteries (Figs. 3, 6, 8) and the variable relation between pulmonary vascular pressure and heart rate (Figs. 2*A* and 2*B*).

In a number of patients and dogs, the intravascular pressure difference between inspiration and expiration exceeded the intrapleural pressure difference considerably (Fig. 1). This would seem to be the case also in the patients with pulmonary hypertension studied by Rodbard.[9] The only group with pulmonary hypertension in his series showing vascular respiratory pressure variation within the usual range expected for the particular disorder was comprised of patients with ventricular septal defect and pulmonary hypertension. In 2 out of 4 patients with cardiovascular disease, vascular respiratory pressure variations also exceeded intraesophageal pressure variations.[10]



A. *B.* *C.*

Fig. 2*B*.—"Respiratory" pressure variations during diffusion respiration in a male dog weighing 25 pounds. There is regular sinus rhythm with no changes in pulse pressure. Tracing from top to bottom: pulmonary artery pressure, right intrapleural pressure, airflow. *A*, Control 2.29 PM. *B*, 2-minute $\bar{p}$ injection of 20 mg. succinylcholine. *C*, 28-minute $\bar{p}$ injection of succinylcholine. (Note the marked pressure variations in pulmonary artery.)

Consequently, the net vascular pressure changes differently in the various segments of the vasculature. The available data show that in segments where vascular respiratory pressure changes are smaller than intrathoracic pressure changes, effective diastolic pressure may remain constant or may even rise in spite of a fall in recorded diastolic pressure during inspiration. During expiration, the conditions are naturally reversed. In segments where the vascular respiratory pressure changes are larger than the intrathoracic pressure changes, the effective pressure falls or rises more than the recorded pressure. This has to be borne in mind for calculations of pulmonary vascular resistance. It has been stressed that changes in pulmonary resistance are difficult to evaluate if the meas-

urements have not been made at comparable distending pressures.[5] Estimating qualitatively the variations of right and left ventricular stroke volume from pressure curves in the absence of intrapleural measurements[11] becomes, therefore, unreliable.

Because the vascular pressure variations are minimal during rapid respiratory rates, these effects are minimized during voluntary hyperventilation. However, the latter introduces all the disadvantages of the nonsteady and nonbasal state.

C. *Central Factors Influencing Vascular Pressures.*—Although usually respiratory pressure variations in the vasculature are explained on the basis of intrathoracic pressure changes,[8,11,12,13] this cannot be true in the above-described cases of pulmonary hypertension, where the vascular pressure variations are in excess of the intrathoracic pressure variations. An additional factor responsible for these respiratory changes might well be the "Traube oscillator," as suggested by Guyton and associates[14] and Dornhorst and co-workers.[1] In his analysis, Dornhorst suggests that oscillation of the vasomotor center is largely responsible for modulation of peripheral resistance, while the variations in stroke volume are caused by the intrathoracic pressure changes. He compares this modulation mechanism to loosely coupled electronic oscillators which are synchronized by the impulse radiations from the respiratory to the vasomotor center, the stretch receptors of the lung, and the receptors in the vascular system between the vena cava and the carotid sinus.

Joels and Samueloff[15] recently described "respiratory" pressure variations in the peripheral vasculature during diffusion respiration induced by succinylcholine.* Demonstrating synchronization of cervical sympathetic and recurrent laryngeal discharges, they proved the irradiation from the active respiratory center to the vasomotor center. On the same basis, they could explain the appearance of sinus arrhythmia during diffusion respiration (Fig. 2*A*). This latter fact indicates that spilling over of impulses from the respiratory center modulates not only vasomotor tone but cardiac activity itself. In our experiments on diffusion respiration, we have found pressure variations of considerably smaller amplitude in the peripheral vasculature than the ones described by the British authors. In 5 out of 13 animals, those variations were seen also in the pulmonary vasculature (Figs. 2*A* and 2*B*). The increase in pulse pressure accompanying the decrease in diastolic pressure during the slow phases of the sinus arrhythmia (Fig. 2*A*) can be explained by the variations in filling time. In Fig. 2*B*, where regular

*The term "diffusion respiration" as used in this paper has been introduced by Draper and Whitehead.[22] It describes the respiratory function in an environment of high O_2 concentration in the absence of respiratory movements. Under these conditions, the O_2 uptake by the pulmonary capillary blood reduces the alveolar O_2 tension and, therefore, the intrapulmonary pressure. The negative intrapulmonary pressure created by the O_2 uptake in the lungs acts as a pump and continuously draws a supply of the ambient O_2 into the lung, thereby providing a sufficient alveolar oxygen tension for full oxygenation of the pulmonary blood. Though this method provides sufficient oxygenation to sustain life without ill effects, it can be applied only over a limited period because no means are provided for the elimination of the excess CO_2. The accumulation of the latter determines the time over which the method can be applied safely. In addition, the following conditions have to be fulfilled for the successful application of the method at the moment respiratory movements are arrested: adequate circulation, patent airways, previous denitrogenation with O_2, and respiratory quotient less than unity.

sinus rhythm is present, there are no variations in pulse pressure. According to Dornhorst, this would mean that no change in stroke volume occurred in this instance. Passive changes of vascular resistance are unlikely in the absence of changes in stroke volume or lung volume. The observation, therefore, represents evidence for active vasomotion.

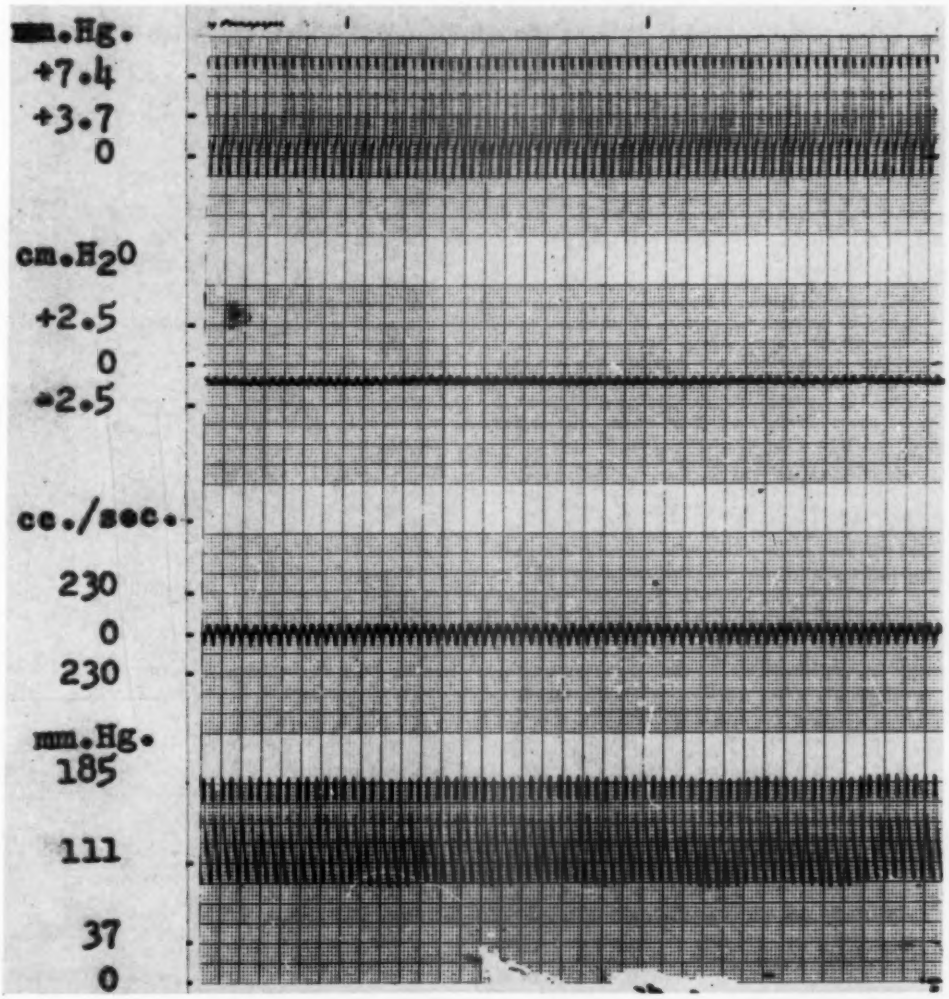


Fig. 3.—"Respiratory" pressure variations in the abdominal aorta but not in the pulmonary circulation during diffusion respiration in a female dog weighing 15 kilograms. Note the respiration variations in femoral artery but not in right ventricle (22-minute $\bar{p}$ 20 mg. succinylcholine). Tracing from top to bottom: right ventricular pressure, right intrapleural pressure, airflow, femoral artery pressure.

These variations seem to occur independent of the initial pressures. Induction of pulmonary hypertension by injection of serotonin did not show any influence upon disappearance or appearance of respiratory pressure variations in the pulmonary vasculature during diffusion respiration. Furthermore, the pressure variations may appear independently in the pulmonary and peripheral

vasculature (Fig. 3). On the basis of these measurements only, it is impossible to determine the relative importance of variations in stroke volume and in vasomotor tone upon the pressure modulations. This problem is at present being investigated.

However, it seems safe to claim that in certain individuals, vascular pressure modulations due to intrathoracic pressure changes are enhanced by the Traube oscillator. The development of sinus arrhythmia during diffusion respiration may indicate that during normal breathing the irradiation from the respiratory center is inadequate to produce sinus arrhythmia. Except when the natural frequency of the Traube oscillator is approached, the central effect on pressure variation also would be small.[1]

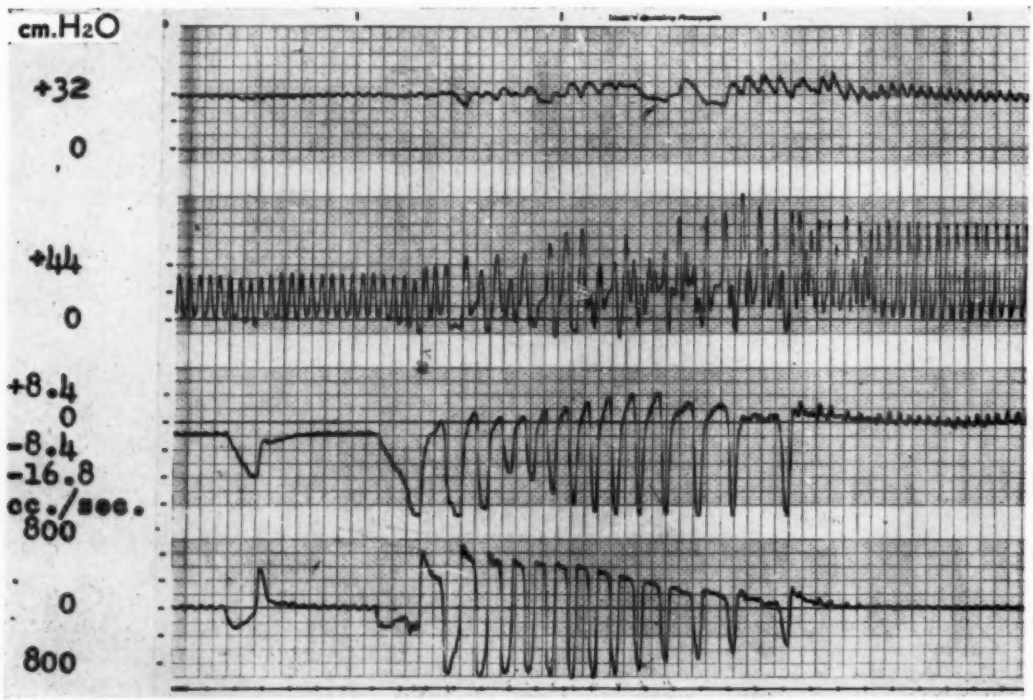


Fig. 4.—Influence of 1.0 mg. of serotonin on pulmonary mechanics in a male dog weighing 10 kilograms. Note the hyperpnea followed by respiratory arrest. Typical response to a single injection of serotonin (100γ/Kg.). There is a transient period of hyperventilation followed by apnea. Right ventricular pressure rises and pulse pressure increases. The pressure fluctuations are also reflected in the spinal fluid pressure. Tracing from top to bottom: spinal fluid pressure, right ventricular pressure, intrapleural pressure, airflow.

D. *Circulatory and Ventilatory Effects of Drugs.*—The evidence cited thus far strongly indicates that respiratory pressure variations in the vasculature depend not only upon intrathoracic pressure changes but also upon a central control mechansim. This problem was further investigated by studying the pulmonary circulatory and ventilatory changes produced by the application of drugs which affect pulmonary function. Although it is well known that Adrenalin increases the vital capacity and reduces the resistance to airflow in patients with

chronic bronchial asthma, there is no agreement as to whether these effects are due primarily to pulmonary vasoconstriction or bronchodilation.[16] The same doubts remain for a number of other drugs, particularly for the opposite acting histamine.

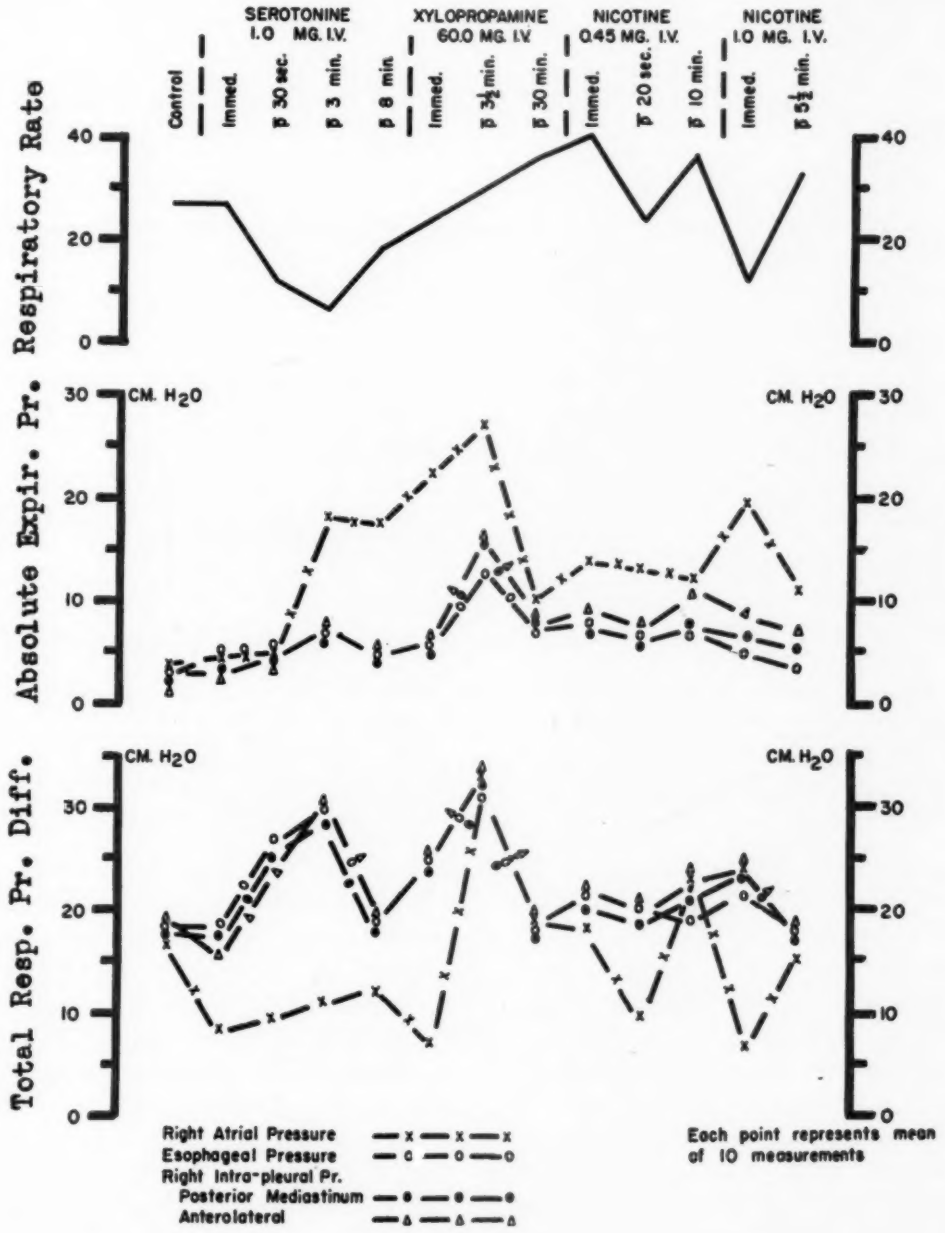


Fig. 5.—Comparison of intrathoracic pressures in a female dog weighing 10 kilograms, under the influence of various intravenously administered drugs. Variations of end-expiratory pressures and total pressure fluctuations in the intrapleural space and the right atrium. Note the dissociated response between pulmonary and vascular pressures after injection of serotonin and nicotine.

The effects of single intravenous injections of serotonin in 12 dogs (100 gamma per kilogram) have been analyzed. In the given dosage, serotonin regularly produced pulmonary hypertension accompanied by a short period of hyperpnea with large intrathoracic pressure swings, followed by a period of apnea (Fig. 4).

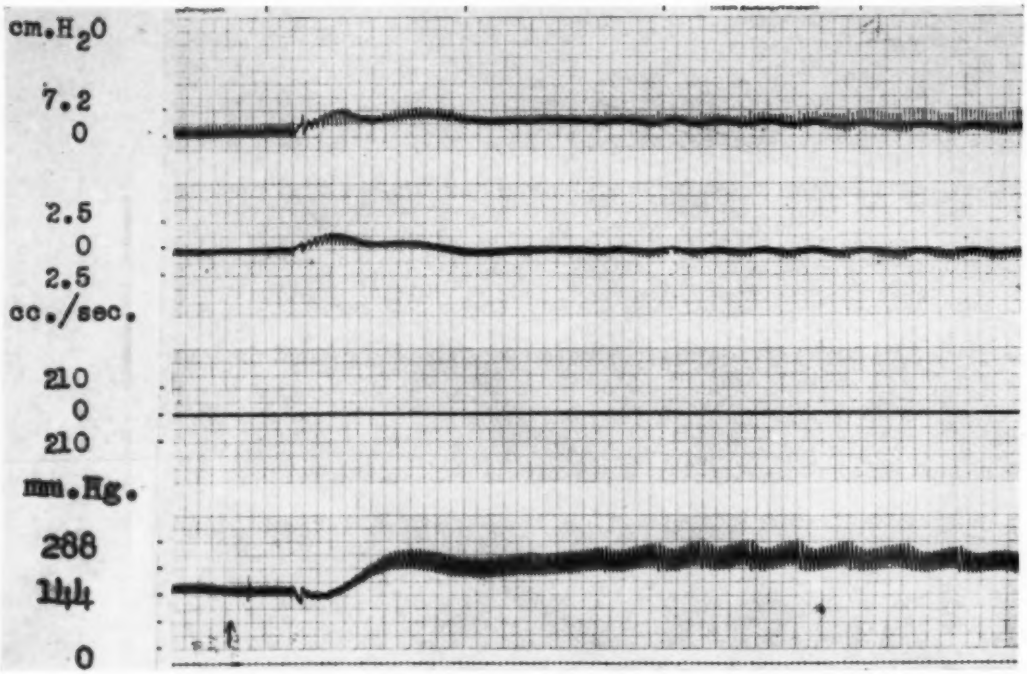


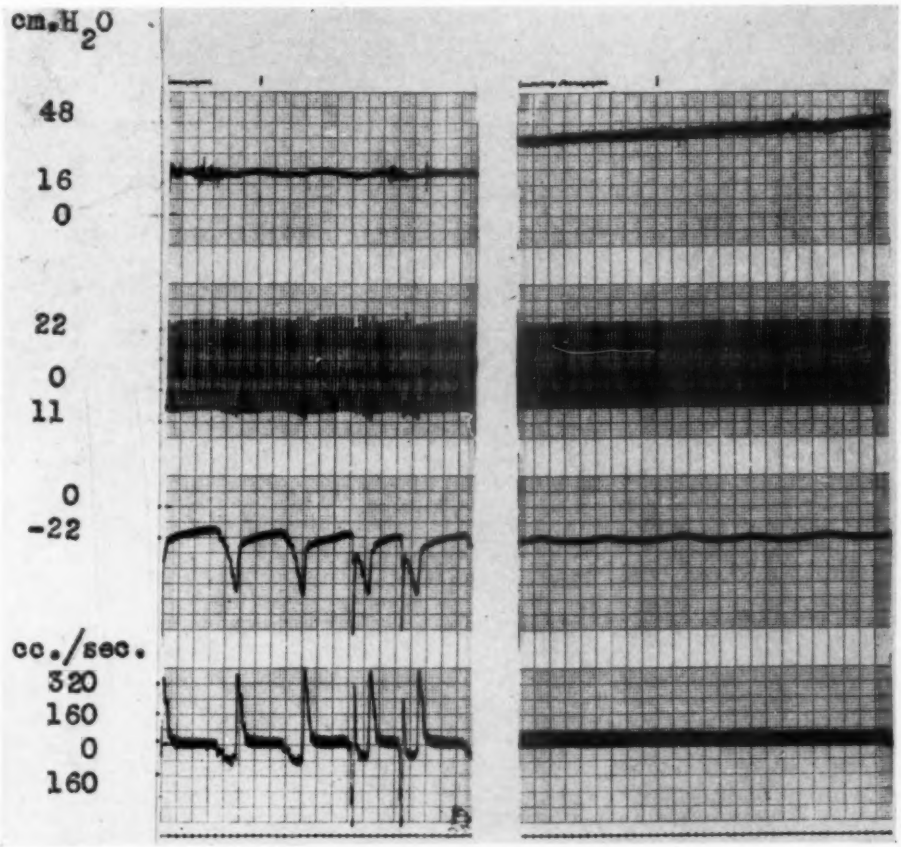
Fig. 6.—Influence of serotonin on circulatory dynamics during diffusion respiration in a male dog weighing 30 pounds (1.5 mg. of serotonin injected intravenously. 2-minute $\bar{p}$ induction of diffusion respiration by 20 mg. succinylcholine). Note the change in intrapleural pressure in the absence of airflow; also, the similar pattern in intrapleural and intravascular pressures and the difference in the response magnitude. Tracings from top to bottom: right atrial pressure, right intrapleural pressure, airflow, aortic pressure.

The end-expiratory intrathoracic pressures increased considerably less than the end-expiratory intravascular pressures, while the reverse was true for the respiratory pressure variations (Fig. 5). Vascular responses in the peripheral arteries were quite variable in contrast to the response of the pulmonary vasculature.

Serotonin is the strongest pulmonary vasoconstrictor known at present.[5] At the same time, it increases cardiac output from 20 to 100 per cent and decreases arterial oxygen saturation considerably, even under artificial respiration.[17] These vascular changes must result in an increased rigidity of the vascular bed. That such changes are not necessarily limited to the vascular bed itself, but may also affect the heart, has been suggested recently by Rushmer.[18] On the basis of measurements of heart size and stroke volume, he concluded that myocardial distensibility and contractibility are influenced by neural and humoral mechanisms.

The vascular effects of serotonin occur also if the drug is applied during diffusion respiration (Fig. 6), and seem, therefore, to be independent of changes in ventilatory mechanics.

Compliance and mechanical resistance usually show a small rise during the initial period of hyperventilation. However, after the apneic interval, there is a marked drop in compliance associated with a large increase in airflow resistance. This indicates that ventilatory changes occur secondary to vascular changes. Similar results have been obtained after embolization of dogs with barium sulfate and with intravenous injection of nicotine.[19] Fig. 6 shows that both intrapleural



A. *B.*

Fig. 7.—Local changes in esophageal tone after induction of diffusion respiration in a male dog weighing 19 kilograms. There is no change in vascular pressures. Tracing from top to bottom: spinal fluid pressure, right ventricular pressure, esophageal pressure, airflow. *A*, Control state. *B*, 2-minute induction of diffusion respiration with 20 mg. succinylcholine. Note pressure variations in esophageal tracing in the absence of corresponding airflow rates.

and right atrial pressure change in the same direction. The change in atrial pressure is about twice as large. Because there is no exchange of air between the lungs and the atmosphere, as demonstrated by the pneumotachogram, the elastic force of the lung must change. This could be due either to a change in intrathoracic blood volume, a change in surface tension forces, or possibly a change in tone of the smooth muscles within the lung.[20] The appearance of parallel rhythmic changes in intrapleural, right atrial, and aortic pressures is striking. However,

the magnitude of these pressure changes is quite different, the vascular changes being roughly 2½ and 25 times greater than the intrapleural changes. It is difficult to explain this phenomenon other than by cyclic variations of smooth muscle tone regulated by a common central mechanism. In Fig. 7, the same type of cyclic pressure variations after induction of diffusion respiration can be seen in the esophageal pressure tracing. There is no pressure variation in the right ventricular tracing, indicating a purely local phenomenon of rhythmic change in esophageal tone.

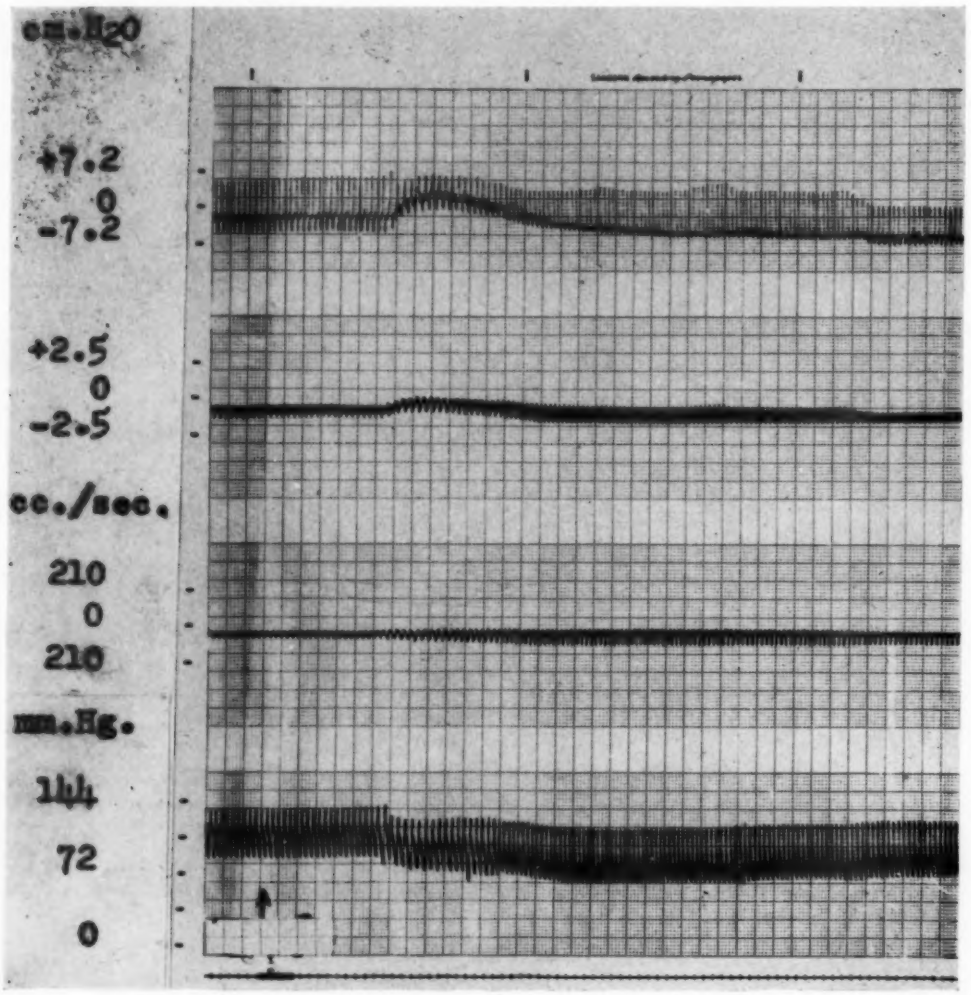


Fig. 8.—Influence of aminophylline on circulatory dynamics during diffusion respiration in a male dog weighing 20 pounds. (Intravenous injection of 250 mg. aminophylline. 8-minute $\bar{p}$ induction of diffusion respiration by 20 mg. succinylcholine.) Note the similarity of right atrial and intrapleural pressure response although the response magnitude is different. Increased stroke volume produces larger airflow rates. Tracing from top to bottom: right atrial pressure, right intrapleural pressure, airflow, aortic pressure.

VENTILATORY EFFECTS UPON CIRCULATION

In the preceding paragraphs, we were mainly concerned with the effects of ventilation upon circulation. In Fig. 8, the circulatory effects on airflow are demonstrated. After induction of diffusion respiration in a dog, 250 mg. of aminophylline was injected, resulting in a characteristic drop in peripheral arterial pressure. The intrapleural pressure again follows the vascular pressures in the right heart: a transient increase followed by a slight drop in pressure, the intrapleural changes being considerably smaller than the vascular changes. The occasional abrupt changes in expiratory pressure observed by Farhi[21] could be due to a similar mechanism. The airflow pattern is synchronized with heart action and is characterized by a marked increase of airflow after the injection of the drug. These airflow rates in the absence of respiratory intrathoracic pressure changes are produced by differences in instantaneous thoracic inflow and outflow of blood, i.e., the differences between stroke volume of the left heart and venous return into the right atrium at a given moment. Cardiac systole is associated with inspiratory flow, and diastole with expiratory flow. The increase of airflow rates after the injection of aminophylline, in the absence of respiratory movements, is due probably to an increase in stroke volume. Though the volume of air exchange due to cardiac activity is physiologically insignificant in most instances, it may become of some importance in patients with severe hypoventilation, by promoting better distribution of the inspired air.

SUMMARY

1. Respiratory intrathoracic pressure variations can produce vascular pressure changes by modulating the stroke volume.

2. Rhythmic vascular pressure variations, synchronous with respiration, can also be produced by a central mechanism through changes in vasomotion and/or stroke volume (Traube oscillator).

3. Respiratory pressure variations vary in different segments of the vasculature, depending upon the physical characteristics of the vascular bed.

4. The net effect of these pressure modulations can result in vascular pressure changes exceeding intrathoracic pressure changes. This seems to be the case in patients with pulmonary hypertension. Its effect upon vascular net pressures is discussed.

5. Changes in the relation between vascular and intrathoracic pressure variations allow differentiation between ventilatory and circulatory changes in the lung.

6. During diffusion respiration, "respiratory" pressure variations can be observed both in the peripheral and pulmonary vasculature. These changes may be coupled with sinus arrhythmia, demonstrating the influence of the respiratory center upon cardiac and vasomotor activity.

7. The application of drugs during diffusion respiration demonstrates their effect upon pulmonary circulation in the absence of ventilation, and the influence of circulatory changes upon static intrapleural pressure (lung elasticity) and air exchange due to cardiac activity.

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SIX MONTHS' TO SIX YEARS' EXPERIENCE WITH CORONARY ARTERY INSUFFICIENCY TREATED BY INTERNAL MAMMARY ARTERY IMPLANTATION

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IN THE year 1945, it was discovered at McGill University that a chest wall artery—the internal mammary artery—could be successfully transplanted into the heart of an animal. During the following 5 years experimental evidence was gathered by Vineberg and associates,[1-4] which showed that the transplanted artery sends out branches which join with the arterioles of the heart muscle (Figs. 1, 2, and 3).

Through these mammary-coronary anastomoses blood may flow in quantities large enough to relieve artificially produced myocardial ischemia. The persistence of these branches, as well as the patency of the implanted internal mammary artery, has been proved.[5]

Human coronary arteries develop disease with occlusion in the epicardial proximal parts of these vessels, leaving a relatively normal distal arteriolar network within the myocardium.[6,7] An implanted internal mammary artery by-passes the proximally blocked vessels and through mammary-coronary anastomoses supplies arterial blood to this intact distal arteriolar network. If intercoronary anastomoses have developed, as suggested by Zoll,[8] then fresh blood should reach all parts of the left ventricle.

On the basis of this experimental and pathologic background, the first human case suffering with angina decubitus was operated upon in April, 1950, at the Royal Victoria Hospital in Montreal. Since that time, 53 patients with disabling angina pectoris have been treated in 5 different Montreal hospitals by internal mammary artery implantation.

On June 11, 1951, Dr. James Walker of Boston, Massachusetts, and Charleston, West Virginia, came to observe our technique in internal mammary artery implantation and to evaluate the experimental and clinical evidence. Since his return, Dr. Walker has performed the internal mammary artery implant operation on 35 patients suffering with angina pectoris due to coronary artery disease. The two series of cases (those operated upon in Montreal and those in Boston and Charleston) have been studied as a single group of 88 patients. These patients have been followed from 6 months to 6½ years by two different groups of cardiologists. Some extremely "bad risk" patients were operated upon early in the series.

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SELECTION OF PATIENTS

In 1950, at the start of the procedure on human cases, the surgeon was given no opportunity to select his patients. Cardiac surgery was considered extremely experimental and hazardous. The only patients who reported for surgery were desperate, disabled, and pain-ridden people.

Fig. 1.—Digestion Vinylite cast made by injecting left coronary artery, coronary sinus, and internal mammary artery with plastic. Note how after 12 days the implanted internal mammary artery has started to bud, but as yet has not formed a mammary-coronary anastomosis. (See arrow.)

Experience quickly showed that the proper selection of a patient for internal mammary artery implantation was largely dependent upon the stage of his coronary artery disease. Many changes in points of view have occurred since 1950, but the surgeons and our cardiological associates are agreed upon the following criteria for internal mammary artery implantation:

Indications.—

1. Proved coronary artery disease with typical angina pectoris pain.
2. Failure to improve within 1 to 2 years with medical treatment.

Contraindications.—

1. *Left ventricular failure:* Patients with left ventricular failure due to coronary artery disease can expect little help from any type of myocardial re-

vascularization. Even though the left ventricular failure is controlled, the ventricular myocardium is usually damaged too much to benefit from fresh extracardiac sources of blood.

2. *Active disease:* Evidence of smouldering coronary artery disease as indicated by the clinical history, electrocardiogram and sedimentation rate.

3. *Recent coronary occlusion with infarction:* An arbitrary waiting period of 6 months has been set after a coronary artery occlusion with infarction. It is hoped that after this period of time satisfactory stabilization of the infarcted area will have occurred.

4. *The presence of associated disease:* Associated diseases include essential hypertension, severe diabetes, etc.

5. *Asymptomatic coronary artery disease:* Every patient with coronary artery disease should not be advised to have revascularization surgery. Patients

Fig. 2.—Digestion Vinylite cast made in same manner as cast shown in Fig. 1. Observe numerous branchings of internal mammary artery present at the end of 5 months. (See arrows.) Flow studies showed a flow rate of 21 c.c. per minute, which increased to 51 c.c. per minute when pressure differentials were increased. Note this implanted internal mammary artery was left in an ischemic animal's heart.

who suffer coronary artery occlusion with infarction, and who have no residual anginal pain, do well as a general rule. According to White,[9] 82 per cent of such patients can expect to be alive at the end of 5 years. The hearts of such patients are well taken care of by their own "good neighbor" arteries, and there appears to be no need for extracardiac sources of blood. Any form of revascularization surgery on such a group of patients can do nothing more than has already been done by nature. To operate as a prophylactic measure at this stage, in our experience, is wrong. The operation may cause the patient harm, and certainly if there is no anginal pain then there is no way in which the results of operative procedure can be evaluated in this particular group of patients.

Fig. 3.—Shows Vinylite cast made by injecting internal mammary artery 7 months after implantation. The large branches coming from the internal mammary artery are clearly seen fusing with the arterioles of the ventricular myocardium. This artery was left in an ischemic animal's heart.

EVALUATION OF RESULTS

There is probably no medical condition, treated by surgical means, in which it is so difficult to evaluate the effect of the operative procedure as in coronary artery disease. In dealing with other types of heart disease, objective evidence of the benefit of surgery is readily obtainable by x-ray evidence of diminution in heart chamber size, and by lowered intracardiac pressures following the opening of an obstructed intracardiac valve. Such changes are readily measurable, and

it is possible to study objectively the results of heart surgery without reliance upon the subjective evidence submitted by the patient. When dealing with patients suffering from coronary artery insufficiency, objective evidence is much more difficult to assess. Postoperative exercise tolerance appears to be the best guide of operative benefit. However, even this may show improvement for a few months after surgery, although subsequent events indicate that the patient has experienced no benefit from internal mammary artery implant. Patients suffering from angina pectoris frequently convey marked subjective improvement after heart surgery, which, in our experience, does not persist beyond 6 months when the improvement has been merely psychologic. It is for this reason that it is best to wait 6 months after operation before attempting to decide how much benefit the patient has obtained.

Before evaluating the result of a surgical procedure such as the internal mammary artery implant, or any other revascularization procedure, it is important to know the patient thoroughly before and after surgery. Careful questioning of a patient by at least three members of a medical team, which includes a psychiatrist, records without prejudice preoperative details of the patient's complaints and objective findings. This is extremely important in patients suffering form coronary artery insufficiency, particularly when so frequently their only symptom is that of anginal pain. Electrocardiographic evidence is helpful, but not conclusive. The time has come for all those interested in the treatment of coronary artery disease to develop a standardized classification of the disease. When this is done, the reported results of therapy—be it medical or surgical—will refer to the same type of case. The mortality from any type of revascularization surgical procedure will vary according to the severity of the coronary artery disease. In a like manner, so will the results of the procedure. On previous occasions the Montreal group has pointed out the futility of expecting to help cases in which the myocardium has been largely replaced by fibrous tissue. No matter how much fresh arterial blood is brought to such a heart, the destroyed myocardial fibers cannot be reconstituted nor can the fibrous scar tissue be made to contract. There is a point of no return for every heart. Comparison between surgical methods used in the treatment of coronary artery disease is thus very difficult unless similar types of cases are being considered. This, likewise, is true of so many reported series of medically treated groups, which accounts for the great variety of treatments that have been accepted enthusiastically only to be discarded in favor of another procedure.

In this series of 88 patients suffering from coronary artery disease, the patients have been divided into two main groups: those who have angina decubitus, and those who have not. In the literature there is a great deal of confusion as to when a patient falls into the angina decubitus class. It is simple if only those cases that have anginal pain at rest without exciting cause are classified as "angina decubitus." For example, patients who are awakened at night with anginal pain are not necessarily those who have reached the angina decubitus stage. Many patients in our series who did not have angina at rest experienced night pain, or pain at rest, while talking on the telephone, watching television, etc. The patients in our series who were classed as "angina decubitus" were all

disabled, all experienced pain at rest without exciting cause, most consumed 200 to 300 nitroglycerin tablets per week, and many entered the hospital in wheel chairs. None could walk, even a few steps, without first placing a nitroglycerin tablet under the tongue. This type of patient is an exceptionally poor operative risk. Those who died did so within a few days of operation from a fresh coronary artery occlusion, the freshly occluded coronary artery being the only vessel open in the heart. Pathologic study of these hearts invariably showed heart muscle to be largely destroyed and replaced by scar tissue, with usually one patent vessel, pin point in size. It is easy to understand when one looks at a heart so destroyed why this type of patient is such a high operative risk. These hearts have such low myocardial reserves that the increased work load caused by an anesthetic is sufficient to turn the tables.

Actually, it is possible, in a general way, to compare the results of internal mammary artery implantation in the treatment of coronary artery disease with the results of mitral commissurotomy for the treatment of mitral stenosis. All are agreed that Grades 4 to 5 of mitral cases are poor surgical risks which carry a mortality of from 25 to 40 per cent. Furthermore, the long-term results in such patients has been far from satisfactory. The patient with angina decubitus due to coronary artery disease may be compared in many ways to a Grade 4 to 5 case of mitral stenosis.

MORTALITY

The operative mortality for 88 patients suffering from coronary artery insufficiency who underwent internal mammary artery implantation is shown in Table I. For those 68 patients who had no angina at rest, the operative mortality was 5.8 per cent. In the group of 20 patients suffering from angina decubitus

TABLE I. OPERATIVE MORTALITY IN INTERNAL MAMMARY ARTERY IMPLANTATION (COMBINED VINEBERG-WALKER SERIES)

TOTAL NUMBER OF CASES 88		MORTALITY
No Angina at Rest	68	4 (5.8%)
Angina Decubitus	20	9 (45%)
Total	88	13 (14.7%)

Compares favorably with operative mortality of 7 per cent reported by Dana and Ohler[10] for patients with the anginal syndrome undergoing general surgery.

there was an operative mortality of 45 per cent. The mortality for the entire series, including the bad risk angina decubitus patients, was 14.7 per cent. Actually, the mortality of 5.8 per cent for the group of patients with no angina at rest is lower than that reported by Dana and Ohler,[10] who surveyed the operative mortality in cardiac patients undergoing general surgery. Heart deaths for the entire series was 2.2 per cent, but for patients with a preoperative anginal syndrome undergoing gerneral surgery the operative mortality was 7 per cent. Thus,

the mortality rate for internal mammary artery implantation in 68 patients without angina at rest is about the same as that of patients suffering angina pectoris who undergo general surgery.

RESULTS

No Angina at Rest.—Of the 68 patients with no angina at rest, 49 or 72.1 per cent were totally disabled before internal mammary artery implantation. Of the entire group, 54 patients returned to work after operation, or 79.4 per cent. There were 53 patients (77.8 per cent) of this group who after internal mammary artery implant were free of pain, or had slight or less pain.

There have been 4 late deaths, 4 months to 4 years after implantation. Two patients died of right coronary artery occlusion. Two patients who had improved and returned to work died suddenly. One, while pushing a car out of the snow, ruptured an old scar in his interventricular septum. The other died suddenly while riding horseback on a hot day on a western ranch. Sixty of the original 68 patients are still alive (88 per cent), and 50 (77 per cent) are working—6 months to 6 years after surgery.

Angina Decubitus.—Of the 20 patients suffering from angina decubitus, all were disabled; most of them were bed-to-chair invalids; many had been sick for 10 to 13 years. Seven of the 20, or 35 per cent, since the operation have no pain, less or slight pain; 6 (30 per cent) have returned to work.

Long-term follow-up of the cases with angina decubitus showed that 9 (45 per cent) of the original group are still alive and that, of these, 5 (20 per cent) are at work.

The difficulty of evaluating the beneficial results of internal mammary artery implant has been pointed out. Many apparently good results have been questioned because of lack of objective evidence other than improved exercise tolerance and ability to work. However, when a bed-chair invalid of the angina decubitus type, using 300 nitroglycerin tablets per week, after internal mammary artery implantation becomes pain-free and returns to work, it suggests that the implanted artery has contributed fresh blood to the ischemic myocardium. This is particularly true if such a patient should die after 18 months from cancer of the pancreas, and examination of the heart shows the internal mammary artery widely open and branching within the myocardium, as was the case with one of our patients, Mr. C. A. (see Fig. 4). It seems fair to assume that blood was flowing from the internal mammary artery into the myocardium in such a case, helping to relieve myocardial ischemia, thus increasing the patient's exercise tolerance and explaining the disappearance of his pain.

Apparent Relationship Between Duration of Anginal Pain and Results of Internal Mammary Artery Implantation.—Hill, of the Montreal group, who followed our patients medically, made a careful study of the 39 patients operated upon at the Royal Victoria Hospital in Montreal. His thoughts on the relationship of survival after operation and duration of disease were applied to the entire Montreal group of 53 patients. Hill pointed out that there appeared to be a relationship between the duration of the disease and the ability of the patient to

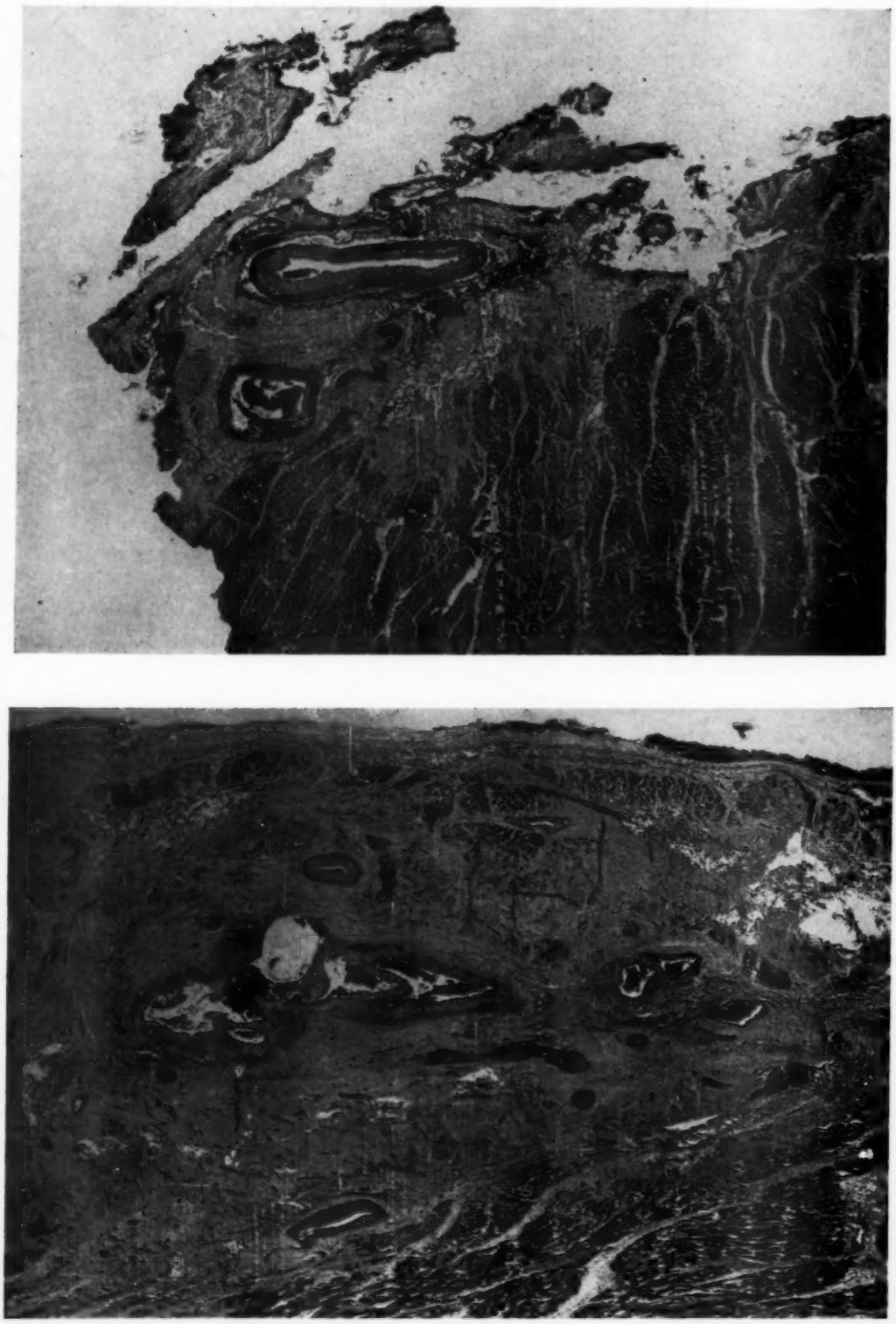
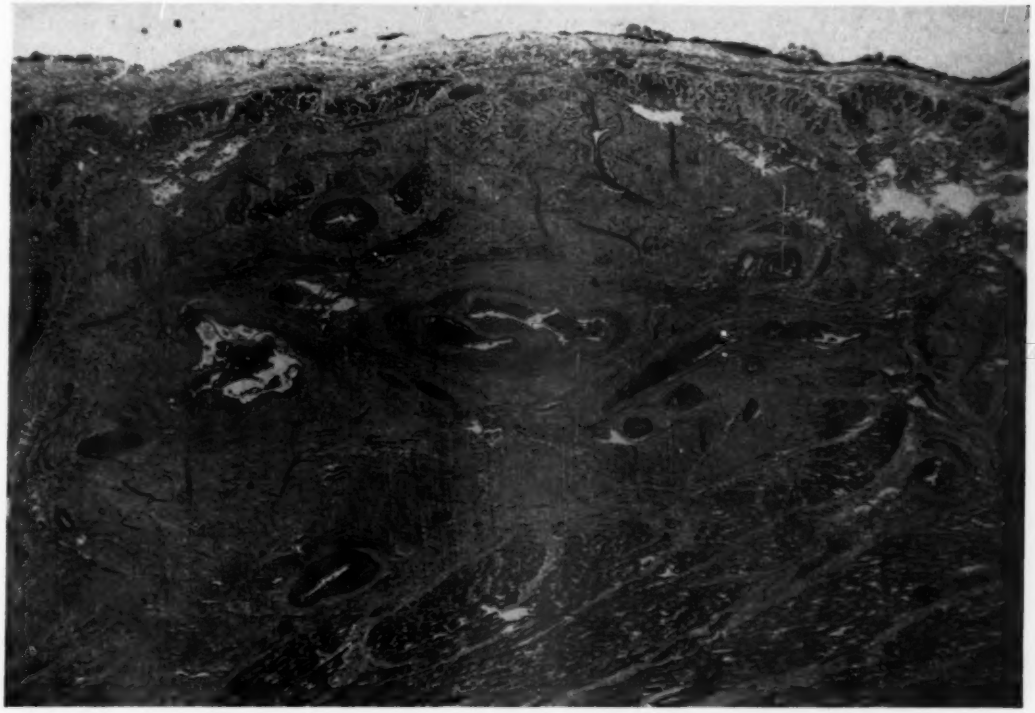


Fig. 4.—Serial microphotographs of heart of Mr. C. A., a 60-year-old man suffering from angina decubitus who completely recovered, was pain-free, and returned to work. He died 18 months later from a cancer of the pancreas. *A*, Shows implanted internal mammary artery at entrance to tunnel. Note absence of intimal proliferation 18 months after implantation. *B*, Internal mammary at ⅓ of the way along myocardial tunnel, branching freely and filled with india ink injected retrograde through the circumflex artery.



C.

D.

Fig. 4 (continued).—*C*, Halfway along myocardial tunnel, many branches. *D*, Near exit of tunnel showing implanted internal mammary still branching through myocardium and widely open.

survive operation and, what is even more important, to return to normal activity after surgery. In Table II this observation is well supported. The angina decubitus group of patients with a high mortality rate had suffered anginal pain on an average of 112.5 months before undergoing internal mammary artery implantation. This group formed a marked contrast to those patients who had no angina at rest, and in whom the symptoms of angina pectoris had been present on an average of 33.3 months. In this latter group there was a low mortality rate and the results were excellent. It is important to note that those patients who died from the operation had suffered their disease for an average of 82.2 months at the time of operation.

TABLE II. DURATION OF DISEASE IN RELATIONSHIP TO OPERATIVE AND POSTOPERATIVE SURVIVAL

53 CASES—MONTREAL GROUP	AVERAGE DURATION OF DISEASE AT TIME OF OPERATION	
	Months	
Angina Decubitus	112.5	High mortality Poor recovery
No Angina at Rest	33.3	Low mortality Good results
Operative Deaths	94.6	
Died Since Operation	82.2	
Still Alive	45.2	

The relationship between the duration of coronary artery disease and the ability of the patient to survive and improve after internal mammary artery implantation seems highly suggestive. On many previous occasions it has been pointed out how important it is to preserve the myocardial fibers. Prolonged and continued myocardial ischemia results in myocardial fiber death and replacement by scar tissue. Gradually, over 10 to 13 years, the heart muscle is slowly replaced by scar tissue. In the hearts of those patients with angina decubitus in the Montreal series who died following operation, there was marked myocardial fiber loss. In effect, there was insufficient myocardial muscle left to carry the heart through the strain of an anesthetic. Moreover, there was actually very little healthy myocardial muscle left to revascularize. The myocardial fiber "bank account" with which the patient had been born had, in every instance, been almost completely dissipated. A good example of the futility of any type of revascularization surgery in far advanced cases of coronary artery disease is demonstrated in Fig. 5. This patient, with angina decubitus and left ventricular failure, had an internal mammary artery implantation successfully performed upon him by a Montreal colleague. Four months later the patient died of progressive heart failure, and without relief of pain. The internal mammary artery was injected with methylene blue which entered the vessels of the myocardium. In this case, the only muscle left in the heart was a thin superficial layer into which the internal mammary

artery had been placed. The rest of the heart was composed of thick scar; nothing could have restored this patient's myocardial fibers—his myocardial bank account had been closed out.

It is our belief that patients suffering with angina pectoris due to coronary artery disease should be offered internal mammary artery implantation before it is too late, before there is little or no myocardium left to revascularize. The operative risk in properly selected and in prepared patients is no greater than for a thoracotomy, and the results are most gratifying. It is for this and other reasons

Fig. 5.—Photograph of serial cross sections of left ventricle in a human case of severe angina with left ventricular failure. Patient died of left ventricular failure 4 months after implantation. Note that the internal mammary artery was injected with methylene blue which entered the left ventricle. Observe the small layer of myocardium on the outer surface of the heart. This is shown at the top of each section. The remaining $^{9}/_{10}$ of the thickness of the ventricular wall is composed almost entirely of scar. The internal mammary artery had been placed in what small amount of muscle there was left. This patient demonstrates that after myocardial replacement by scar it is too late to expect any form of revascularization surgery to benefit a heart so destroyed.

that a waiting period of 1 to 2 years after the onset of anginal pain is suggested, beyond which operation should not be postponed. Undue delay is just as dangerous as is the practice of revascularization surgery on patients who are asymptomatic and whose only fault is to have had a small coronary thrombosis.

A few characteristic cases might be worth mentioning.

The Montreal group reports: (1) An oil prospector operated upon at the Royal Victoria Hospital in November, 1950, could walk through the bush for miles with a pack sack after opera-

tion. (2) A Grey Nun nursing sister who, 2 years prior to operation, was totally disabled by angina decubitus was admitted to the Montreal Heart Institute where she underwent internal mammary artery implantation. She is now pain-free and working a full day. (3) A patient who is 4 years postoperative now plows 1,600 acres.

The Charleston, West Virginia, group reports: 3 coal miners after internal mammary artery implantation are pain-free or have slight pain. These men have returned to work in the coal mines. Another patient is driving a truck, 5½ years after internal mammary artery implant.

CONCLUSION

Eighty-eight patients suffering from angina pectoris due to coronary artery disease have been treated by internal mammary artery implantation. In those patients with no angina at rest the mortality is low, 5.6 per cent, and the over-all results are excellent. Seventy-two and one-tenth per cent of the patients were disabled before surgery and 79 per cent returned to work. Seventy-three and three tenths per cent of this group were pain-free, or had slight or less pain. The results in those patients who had suffered from the disease for a long time were generally not satisfactory. The optimum beneficial results seem to be obtained in patients who have been suffering, on an average, for 33 months. Excellent results have been obtained up to 45 months.

Delay in the surgical treatment of coronary artery disease may result in so much destruction of heart muscle that an attempt at revascularization is futile.

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THE ROLE OF DIGITALIS IN MITRAL VALVULOPLASTY

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IN REVIEWING the experiences we had with the first 50 consecutive patients selected for mitral valvuloplasty, it became apparent that the digitalis preparations played a major role in their preoperative and postoperative medical management. The importance of digitalis as a specific prophylactic and therapeutic agent in the management of such patients, and the reservations regarding the need and use of digitalis preparations[1] make it important to report our detailed initial experiences upon which our subsequent medical regimen has been based.

METHOD

The patients were divided into 6 different categories (Table I). The grouping was based on the following factors: absence of preoperative digitalis administration; inadequate digitalis prior to surgery; inability to tolerate anesthesia until further digitalis therapy was employed; prolonged digitalis intake prior to surgery; surgical exploration without valvuloplasty; and death.

RESULTS

GROUP 1: *No Digitalis Prior to Surgery* (*Table II*).—All 5 patients with regular sinus rhythm, who had taken no digitalis previously, developed auricular fibrillation under anesthesia or during the postoperative period. None had past histories of congestive heart failure or digitalis intake, except for J. C. who received digitalis for a short period 6 years before. Physical examination, venous pressures, and circulation times had revealed no evidence of congestive heart failure just prior to surgery.

Three patients had a history of paroxysmal tachycardia, for which 1 had been receiving quinidine therapy in the preoperative period. Another (J. C.) developed auricular fibrillation and acute left ventricular failure while under anesthesia, causing a postponement of surgery until he was digitalized. The others developed auricular fibrillation with rapid ventricular rates in the postoperative period, controlled with difficulty with large doses of digitalis. In 1 patient the arrhythmia persisted at the time of discharge.

The usual time of onset of the auricular fibrillation was 2 to 4 days postoperatively, although 1 patient (L. J.) developed her arrhythmia on the fifteenth postoperative day. In this patient, however, there was some question of rheumatic activity and Aschoff bodies were found in the auricular appendage.

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TABLE I. SUMMARY OF PATIENT GROUPS

PREOPERATIVE				POSTOPERATIVE		
CATEGORY	NUMBER OF PATIENTS	RHYTHM	AVERAGE AGE (YEARS)	ASCHOFF BODIES	COURSE	AVERAGE ONSET OF COMPLICATIONS
1. No digitalis prior to surgery	5	RSR	32	3	All AF	4 days
2. Inadequate digitalis prior to surgery	10	7 RSR	42	1	All 7 AF; 4 CHF	2 days
		3 AF	37	0	2 rapid rate; 1 CHF	
3. Inability to tolerate anesthesia	4	1 RSR	42	0	AF; CHF; rapid rates able to tolerate anesthesia after more digitalis	anesthesia
		3 AF	41	0		
4. Prolonged digitalis administration	26	11 RSR	35	4	7 uneventful, 4 varied complications (Table IV)	1-2 weeks
		15 AF	41	2	14 uneventful; 1 rapid rate	
5. Exploration without valvuloplasty*	4	AF	34	0	3 uneventful, 1 pneumothorax	none
6. Deaths*	3	AF	42	0	1 hemorrhage; 2 ventricular fibrillation	surgery anesthesia
Total	52	(One patient was included in three categories.)				

*On digitalis during preoperative period.
RSR = Regular sinus rhythm. AF = Auricular fibrillation. CHF = Congestive heart failure.

Case Illustration.—L. R. was a 35-year-old woman with long-standing rheumatic heart disease and mitral stenosis, in regular sinus rhythm; she had a history of increasing dyspnea on effort, recurrent hemoptysis, and transient auricular fibrillation controlled with quinidine. She was classified in Harken's Group 3.[2] Venous pressure and circulation times were normal. The patient came to surgery on maintenance quinidine, 0.2 Gm. 4 times daily, and without any digitalis administration. Mitral valve fracture was performed without incident.

On the second postoperative day sudden auricular fibrillation developed, with a ventricular rate of 210 to 220 beats per minute. Lanatoside C, 1.2 mg. intramuscularly, plus 1.5 mg. of digoxin were administered, with a fall in the ventricular rate to 120 beats per minute. Three days postoperatively auricular fibrillation with a ventricular rate of 90 was present, and 1.0 mg. of digoxin was given orally. On the fourth postoperative day auricular fibrillation at a rate of 80 was present, and 0.25 mg. of oral digoxin was administered. The patient then had an uneventful course, and her rate was controlled with a daily dose of 0.25 mg. to 0.5 mg. of digoxin. Conversion to regular sinus rhythm was later accomplished with the addition of quinidine.

TABLE II. (GROUP 1) NO DIGITALIS PRIOR TO SURGERY

PATIENT	AGE (YEARS)	PREOPERATIVE		POSTOPERATIVE		
		HARKEN GROUP	RHYTHM	ASCHOFF BODIES	RHEUMATIC ACTIVITY	ONSET OF AURICULAR FIBRILLATION
L. J.	19	3	RSR	+	?	15 days
M. V.	25	3	RSR	+	0	2 days
M. F.	38	3	RSR	0	0	4 days
L. R.	35	3	RSR	+	0	2 days
J. C.	42	3	RSR	0	0	Anesthesia

GROUP 2: *Inadequate Digitalis Prior to Surgery* (*Table III*).—Digitalis preparations either administered for the first time from 1 to 16 days prior to surgery, or reinstituted after previous discontinuance, or omitted for several days prior to surgery, to us constituted inadequate digitalization. Ten patients fell into this group. All 7 with regular sinus rhythm developed auricular fibrillation postoperatively, with the majority going into congestive heart failure. Subsequently, 3 of these patients could not be converted back to regular sinus rhythm and were discharged in auricular fibrillation. The administration of quinidine, without digitalis, in the pre- and postoperative periods did not prevent the occurrence of auricular fibrillation on the second postoperative day in patient C. S. Of the 3 patients with auricular fibrillation preoperatively, 1 developed congestive failure in the postoperative period when the ventricular rate became rapid, and another developed a very rapid ventricular rate without further complication. There was no clinical evidence of rheumatic activity in any patient in this group.

Case Illustration.—S. K., a 29-year-old woman with rheumatic heart disease, mitral stenosis, and regular sinus rhythm, was classified in Harken's Group 3. No digitalis had been received, except for a brief period during a pregnancy 4 years before. Two days preoperatively she received a total of 3.0 mg. of oral digoxin in divided doses. Digoxin, 0.5 mg., was then given orally each morning. Potassium Triplex* in 5 c.c. doses 3 times daily was started 2 days preoperatively. Mitral valvuloplasty was performed without incident.

*Potassium Triplex (Eli Lilly & Co.). Each 5 c.c. contains potassium acetate 0.5 Gm., potassium bicarbonate 0.5 Gm., and potassium citrate 0.5 Gm. It is equal to 15 meq. of potassium.

Digoxin 0.5 mg. was continued on the first and second postoperative days. On the second postoperative day auricular fibrillation with a ventricular rate of 180 accompanied by signs and symptoms of congestive heart failure developed. This followed a positive fluid balance of 3,350 ml. and 2,340 ml. on the first and second postoperative days, respectively (Fig. 1). A total of 1.75 mg. of digoxin was administered intramuscularly in divided doses. This was followed by a fall in the ventricular rate to 88 on the following (third) postoperative day, a drop in the positive fluid balance to 590 ml., and clearing of congestive failure. On the third postoperative day 0.5 mg. of digoxin intramuscularly was given at intervals of 12 hours, with a continuation of auricular fibrillation and a ventricular rate in the eighties. Digitalis was omitted on the fourth postoperative day because of nausea and occasional premature ventricular contractions. Here again there was an increase in the positive fluid balance. On the fifth postoperative day digoxin 0.5 mg. orally each morning was started. This was followed by a return to regular sinus rhythm on that day. The patient then had an uneventful course, with a ventricular rate never exceeding 100, and a normal fluid balance.

GROUP 3: *Inability to Tolerate Anesthesia* (*Table I*).—The administration of anesthesia was followed by rapid ventricular rates and signs and symptoms of congestive heart failure in 4 patients. The 3 patients with long-standing auricular fibrillation had been on digitalis therapy. The fourth (J. C.), with regular sinus rhythm, had not had digitalis. In all, a period of intensified digitalis therapy, following the postponement of surgery, allowed these patients to withstand the anesthesia and operative procedure at a later date without untoward effects.

GROUP 4: *Prolonged Digitalis Administration* (*Table IV*).—The most benign postoperative course was found in patients who had been maintained on digitalis preparations for long periods of time prior to surgery. In this group there were 26 patients, all of whom had been taking digitalis for periods ranging from 3 months to 10 years, with an average of 3.8 years. The patients' ages ranged from 27 to 53 years.

Of the 11 patients with regular sinus rhythm, 9 maintained this rhythm in the postoperative period, despite past histories of frequent paroxysmal arrhythmias. Only 1 of the 15 patients with auricular fibrillation developed a transient rapid ventricular rate during the postoperative period, and none had congestive heart failure.

Four patients with preoperative regular sinus rhythm developed increased failure postoperatively, with 2 demonstrating transient auricular fibrillation. One patient showed clinical evidence of rheumatic activity postoperatively, a second had severe electrolyte imbalance attributed to mercurial diuretics administered shortly before surgery, a third had pleural and pericardial effusion with questionable rheumatic activity, and the fourth had primary lung disease as determined by lung biopsy during surgery.

Case Illustration.—Regular sinus rhythm: E. W., a 31-year-old woman with rheumatic heart disease, in regular sinus rhythm, had been maintained on digoxin 0.25 mg. daily for 7 years and on a low-salt diet for 2 years. Her rhythm at times was grossly irregular and she had a history of 2 previous cerebral vascular accidents. She was considered to be in Harken's Group 2. Eight days prior to surgery digoxin was increased to 0.25 mg. twice daily, and potassium Triplex 10 c.c. 3 times daily was initiated. Mitral valve fracture was performed without incident.

Postoperatively, she was continued on digoxin 0.25 mg. twice daily, and potassium Triplex 5 c.c. 3 times daily. Regular sinus rhythm was maintained throughout her entire course, with the ventricular rate never exceeding 100.

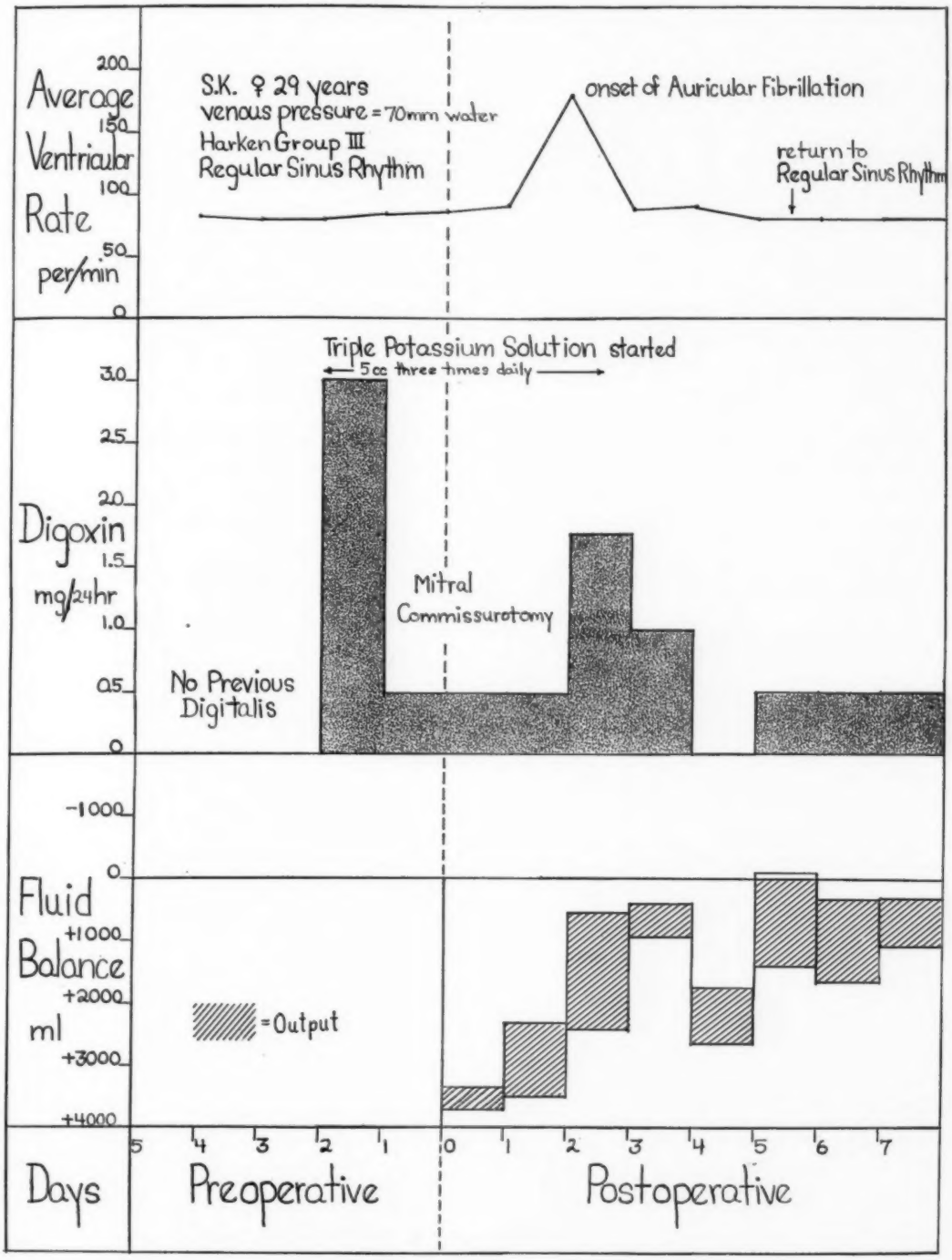

Fig. 1.—Digitalis and fluid balance. The onset of auricular fibrillation and congestive heart failure following the usual postoperative positive fluid balance, in a patient inadequately digitalized preoperatively (first dose 2 days prior to surgery).

TABLE III. (GROUP 2) INADEQUATE DIGITALIS PRIOR TO SURGERY

PATIENT	AGE	PREOPERATIVE				POSTOPERATIVE			
		HARKEN GROUP	RHYTHM	DIGITALIS		ASCHOFF BODIES	RHEUMATIC ACTIVITY	COMPLICATION	DAY OF ONSET
				INITIAL DOSAGE	OMISSION*				
M. In.	50	3	RSR	12 days		0	0	CHF; AF	3; 5
R. J.	32	2	RSR	13 days		0	0	AF; CHF	1
R. S.	39	3	AF	3 days		0	0	AF (rapid); CHF	1
J. C.	42	3	RSR	12 hours		0	0	CHF; AF	0; 6
D. L.	53	2	RSR	20 days (irregular)	2 days	0	0	AF	4
C. S.	39	3	RSR	2 days		0	0	AF	2
F. K.	47	2	AF	30 days	9 days	0	0	AF (rapid)	0
B. E.	47	3	RSR	1 year (irregular)	6 days	+	0	AF; CHF	2; 3
S. K.	29	3	RSR	2 days		0	0	AF	2
Z. T.	26	2	AF	16 days		0	0	None	

*Consecutive days of omission immediately prior to surgery.
RSR = Regular sinus rhythm. AF = Auricular fibrillation. CHF = Congestive heart failure.

TABLE IV. (GROUP 4) PROLONGED DIGITALIS ADMINISTRATION

PREOPERATIVE			POSTOPERATIVE COURSE					
			UNEVENTFUL		COMPLICATED			
BASIC RHYTHM	NUMBER OF PATIENTS	PERIOD ON DIGITALIS	NUMBER OF PATIENTS	ASCHOFF BODIES	PATIENT	ASCHOFF BODIES	PRIMARY DISTURBANCE	RHYTHM
Auricular Fibrillation	15	5 mo. to 10 yr.	14	2	J. J.	0	Transient rapid ventricular rate	Transient rapid ventricular rate—AF
Regular Sinus Rhythm	11	3 mo. to 7 yr.	7	2	M. Im.	+	Pleural pericardial effusion; rheumatic activity?	No change
					J. K.	0	Electrolyte and fluid imbalance; congestive heart failure	No change
					D. G.	0	Primary lung disease	Transient AF
					A. G.	+	Rheumatic activity	Transient AF

AF = Auricular fibrillation.

Case Illustration.—Auricular fibrillation: H. H., a 32-year-old woman with long-standing rheumatic heart disease, mitral stenosis, and auricular fibrillation, was classified in Harken's Group 3. The patient had been maintained on 0.75 mg. of digoxin daily for the past year. Six days prior to surgery it was noted that effort or exercise appreciably increased her resting ventricular rate. Therefore, she was redigitalized with a total of 2.25 mg. of digoxin on the sixth and fifth preoperative days so that no marked rise in her ventricular rate after exercise occurred. A daily dose of 0.75 mg. was then maintained. Mitral valvuloplasty was tolerated without incident.

The postoperative course, except for minimal pleural effusion, was entirely uneventful. Digoxin was continued at 0.75 mg. daily, and the ventricular rate never exceeded 100.

GROUP 5: *Surgical Exploration Without Valvuloplasty* (*Table I*).—Surgery without valve fracture, because of marked mitral insufficiency found at operation, was performed in 4 cases who were on maintenance digitalis. There was no increase in the daily requirements of digitalis postoperatively as compared to the preoperative dosages, even though in 3 of the 4 patients there was evidence of passive congestion of the lungs during surgery and in the pathologic sections. The lack of a need for additional amounts of digitalis postoperatively in this group was in sharp contrast to the usual postoperative supplements required in patients undergoing valvulotomy.

GROUP 6: *Deaths* (*Table I*).—In this first group of 50 patients there were 3 deaths; all 3 were desperately ill patients. One succumbed to a massive hemorrhage from a tear which developed in a very friable left auricle. The other 2 died of ventricular arrhythmias which occurred under anesthesia prior to actual cardiac manipulation. One of these patients came to surgery on large doses of cortisone, digitalis, and potassium. The average daily dose of digitalis was 3.5 mg. of Gitaligin for 4 weeks preoperatively. He was thought to have had rheumatic activity over a prolonged period of time, and surgical intervention with fracture of a markedly compromised mitral valve was considered to be his only chance for survival. The role that digitalis played in conjunction with cortisone, potassium, and possible rheumatic activity in the development of ventricular tachycardia in this patient is difficult to assay. The second patient, who died of ventricular fibrillation, had been on an average daily maintenance dose of 0.75 mg. of digoxin with supplementary potassium preoperatively. A review of his electrocardiograms after death revealed coupling 4 days previously and occasional ventricular premature contractions on the day before anesthesia. This patient may be an illustration of the possible dangers of over-digitalization.

DISCUSSION

The frequent occurrence of postoperative auricular fibrillation in patients with regular sinus rhythm undergoing mitral valve surgery has been documented in other series.[1,3,4] In one group of 374 patients in regular sinus rhythm, 103 of whom did not receive any digitalis preoperatively, 94 developed postoperative auricular fibrillation.[1] In another series, 23 of 95 cases developed this postoperative complication.[3] A third report had 13 episodes of postoperative fibrillation in a group of 48 with preoperative regular sinus rhythm.[4] These are not just transient episodes since 21 of 94 patients in one group[1] and 15 of 23 in a second group[3] were discharged with permanent auricular fibrillation and its consequently

deleterious effects. The occurrence of postoperative congestive failure as a consequence of these rapid arrhythmias was not an uncommon feature.[1] These results, as well as our own, have led us and others[5,6] to practice the routine preoperative use of digitalis in all patients undergoing mitral valvuloplasty.

In our experience, however, routine administration is not sufficient. It is only the prolonged use of digitalis in adequate dosage that appears to afford the myocardium greater protection against the development of arrhythmias and congestive failure in patients undergoing mitral valve surgery. This was demonstrated in our group of 50 patients, of whom 22 had preoperative regular sinus rhythm and 28 auricular fibrillation.

Patients in regular sinus rhythm who received no digitalis, or inadequate amounts of digitalis preoperatively, without exception developed auricular fibrillation in the postoperative period (Tables II and III). This took place regardless of normal venous pressures and circulation times in the preoperative period and regardless of the Harken's groupings. Protection against postoperative auricular fibrillation was afforded 9 of the 11 patients who received prolonged preoperative digitalis administration (Table IV). Of the 4 who developed postoperative complications, 2 had only transient auricular fibrillation. The use of quinidine without digitalis in our series, as in others,[7] did not prevent the appearance of postoperative arrhythmias. That increased myocardial irritability secondary to digitalis did not play a role is demonstrated by the onset of postoperative auricular fibrillation at the same time in the inadequately digitalized group as well as in those who received no digitalis at all. Myocardial irritability during surgery is not reduced by the elimination of digitalis.[6]

Of the 28 patients with preoperative auricular fibrillation, 14 of 15 patients had uneventful postoperative courses after prolonged preoperative digitalis preparation (Table IV). Minimal or inadequate preoperative digitalis administration resulted in rapid ventricular rates and/or congestive failure in all patients in the immediate postoperative period or under anesthesia (Tables I and III).

The presence of Aschoff bodies in the biopsied auricular appendages did not alter the digitalis requirement unless accompanied by signs and symptoms of active rheumatic fever. Of the 10 patients (Table I) who had Aschoff bodies, only 3 showed signs and symptoms suggestive of possible rheumatic activity (Tables II and IV). The remaining 7 patients fell into the previously described general categories. It is of interest that in this series 8 of the patients with Aschoff bodies are in the group with preoperative regular sinus rhythm where the average age is 35.4 years, in contrast to only 2 patients with Aschoff bodies in the auricular fibrillation group where the average age is 40.5 years. This association of regular sinus rhythm, greater frequency of Aschoff bodies, and lower age groups has also been demonstrated by others.[8]

The beneficial results of digitalis may reflect the effects of the drug on several diverse factors. The fracture of the stenosed mitral valve places an increased load on the diseased, often atrophied, left ventricle by increasing left ventricular filling. That this may not take place immediately because of secondary changes in the pulmonary vessels and/or atrophied left ventricle has been demonstrated.[9] The dramatic fall in the pulmonary artery pressures immediately following frac-

ture which is observed in some patients,[9] and x-ray evidence of increased cardiac size,[10] however, reflect the immediate as well as the eventual long-term increase in left ventricular filling and the need for increased cardiac output if the valvuloplasty is successful.

The period of greatest digitalis requirement usually occurred on the second to the fifth postoperative day. Patients who received no digitalis or inadequate amounts usually had their greatest difficulty in terms of increased ventricular rates, arrhythmias, and congestive heart failure during this period. This increasing need closely parallels the fluid retention which takes place postoperatively (Fig. 1), an observation also confirmed by the metabolic studies of Wilson and associates.[11] Thus, retention of fluids during this period may be a precipitating factor for the increased digitalis requirements.

The increased cardiac rate which develops as a result of ether anesthesia, the trauma of surgery, and postoperative side effects are other factors which may create a greater need for digitalis at this time. That the anesthesia and trauma were not the sole factors, however, guiding this need for additional digitalis was demonstrated in the 4 patients who had valvular exploration without fracture and required no additional digitalis postoperatively. In the rheumatic heart, any condition which produces tachycardia frequently impairs the circulatory function by decreased stroke volume output[12] and increased pulmonary blood volume, with the likelihood of pulmonary edema.[13] Under-digitalization may control the cardiac rate at rest but may not prevent a rise with effort[14] or under stress. Four patients who could not tolerate anesthesia because of the development of tachycardia and cardiac failure were able to do so at a later date when additional digitalis was administered.

On the basis of these observations we believe that all patients prior to mitral valve surgery, regardless of the rhythm or lack of evidence of congestive failure, should have prolonged and full digitalization. The maintenance dose that seems to preserve a satisfactory ventricular rate and adequate cardiac compensation with the patient at rest frequently proves to be inadequate when greater stress, such as surgery, occurs. Therefore, we are now employing the patient's ventricular response to exercise during the preoperative preparatory period as an important criterion for adequate digitalization.

The digitalis preparations most frequently employed in the immediate postoperative period were lanatoside C and digoxin. The short latent period of lanatoside C and the more prolonged effects of digoxin, together with their relatively rapid elimination,[15,16] made these agents the drugs of choice. With rapid ventricular rates and/or congestive failure, lanatoside C was administered intravenously or intramuscularly in doses of 0.4 mg. to 0.8 mg. at intervals of 4 to 6 hours. Digoxin in 0.5 mg. doses was given as soon as the rate or failure was controlled, or concomitantly with lanatoside C parenterally, for more prolonged effects and continued digitalization. The addition of lanatoside C and/or digoxin to the usual postoperative intravenous fluids was found to be a rapid, effective, and safe method of administration. The parenteral route appeared to eliminate or reduce the amount of nausea and vomiting as compared to the oral administration of equal doses of digitalis postoperatively when the intake of food and liquid was limited.

In the preoperative period digitalis usually was administered orally in the form of digoxin, except when patients had been previously maintained satisfactorily with other digitalis preparations. Occasionally the administration of Gitaligin has allowed the use of larger amounts of digitalis without toxic manifestations.[17] More often potassium salts orally and parenterally during the pre- and postoperative periods have enabled us to avoid toxic manifestations while increasing digitalis intake.

The beneficial effects of potassium in digitalis toxicity has been amply demonstrated.[18,19,20] Since the urinary output is often curtailed for several days postoperatively, allowing for possible potassium accumulation, constant observation of the level of the serum potassium and the fluid output is necessary. The elevation of serum potassium following mitral valvuloplasty, and most surgical procedures, secondary to the release of intercellular potassium, has been noted by others.[11]

In addition to digitalis and potassium, the usual methods for the management of congestive heart failure were employed. This included bed rest, low-salt diets, mercurials, and resins. Our experience with patients on low-sodium diets, who received several mercurials shortly before surgery and developed markedly low blood sodiums postoperatively, emphasized the dangers of too vigorous diuresis. The loss of sodium, plus the postoperative dilution secondary to fluid retention, can lead to severe hyponatremia.[21]

SUMMARY AND CONCLUSIONS

Experiences in regard to digitalis requirements with 50 patients selected for mitral valve surgery are detailed. Auricular fibrillation, often accompanied by congestive heart failure, developed postoperatively in all patients with regular sinus rhythm who received no digitalis or inadequate amounts of digitalis during the preoperative period. Rapid ventricular rates and congestive heart failure occurred, with but one exception, under anesthesia or during the postoperative period in patients with preoperative auricular fibrillation who received short-term or inadequate digitalis preparation. The use of quinidine, unless accompanied by digitalis, did not prevent the appearance of postoperative arrhythmias. The most benign postoperative course was noted where adequate long-term digitalis therapy had been present.

The use of potassium helped prevent toxic manifestations when increasing digitalis intake. The parenteral administration of digitalis during the immediate postoperative period appeared to eliminate or decrease the amount of nausea and vomiting as compared to that occurring when equivalent oral amounts of digitalis were attempted. The patients' ventricular response to exercise during the preoperative preparatory period as an important criterion for adequate digitalization is suggested.

A number of the adverse factors occurring subsequent to mitral valve surgery are discussed. The increased need for digitalis may reflect the increased left ventricular filling following valve fracture, the decrease in stroke volume output consequent to tachycardia, and the positive fluid balance occurring postoperatively.

It is concluded that long-term digitalis administration in larger than usual maintenance dosage affords the myocardium greatest protection against arrhythmias and congestive heart failure in patients undergoing mitral valve surgery. It is recommended that all patients prior to mitral valve surgery, regardless of the rhythm or lack of evidence of congestive failure, have prolonged and full digitalization.

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THE T-a WAVE OF THE ADULT ELECTROCARDIOGRAM: AN EXPRESSION OF PULMONARY EMPHYSEMA

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THE T-a wave of the adult electrocardiogram has been considered devoid of clinical or pathologic significance, being held as the repolarization process of the auricular mass. Stimulated by a recent report by Gross,[1] in which he found exaggerated T-a waves in 10 instances of cor pulmonale, we have studied 2 large series of patients who showed exaggerated T-a wave depression on routine electrocardiographic survey. The presence or absence of pulmonary emphysema was determined on these patients by chest x-ray and pulmonary function tests. Sixty additional patients with clinically established, moderately severe to severe pulmonary emphysema or chronic cor pulmonale were also studied for the presence or absence of significant T-a wave depression. The degree of T-a wave depression was correlated in these studies with the patient's age, cardiac rate, P-wave amplitude and duration, P-R interval and cardiac position.

A broad difference of opinion in roentgen interpretation of existing pulmonary emphysema has been recognized generally. An ancillary purpose of this report is to compare the pulmonary function data with chest roentgenographic interpretation as they pertain to the recognition of pulmonary emphysema.

The use of the term, T-a wave, is somewhat ambiguous, for, in fact, one is measuring only the proximal portion of the T-a wave, represented as the P-Ta segment. Common usage, however, has led to the adoption of the term T-a wave. Only electrocardiograms with T-a wave depressions of 0.5 mm. or more in standard Lead II were selected for the present study, in order to exclude those falling within the accepted normal range of T-a wave depression.[2-5]

MATERIALS AND METHODS

Group I.—One thousand nine hundred and twenty electrocardiograms were available on routine admissions to the Veterans Administration Hospital, Madison, Wisconsin. Most of the patients were hospitalized for treatment of pulmonary disease, and many presented advanced stages of pulmonary emphysema. From this series, 133 were initially selected who showed T-a wave depression of 0.5 mm. or more in standard Lead II, irrespective of cardiac rate. They were categorized subsequently according to patient's age, heart rate, P-wave amplitude and duration, P-R interval, cardiac position, and the presence or absence of pulmonary emphysema as detected

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by chest roentgenographic interpretation and pulmonary function testing. Included in the test program were the vital capacity, timed vital capacity, maximum breathing capacity (noting whether the latter test was performed at the hyperinflation level, depicted as E), and the single breath oxygen test.[6] In approximately ½ of the study group, the index of intrapulmonary mixing and the residual volume determinations (R.V./T.L.C. × 100) were also available. Test criteria are shown in Table I, and were classified as none, minimal, moderate, or severe emphysema. Roentgenographic impression for the presence or absence of generalized pulmonary emphysema was established by one examiner (J.H.J.). These criteria are shown in Table II. The degree of pulmonary emphysema was also graded as none, minimal, moderate, or severe. The grading was an opinion or impression of the examiner, since all of the signs noted in Table II were not present in each patient and one or several signs often predominated in a given patient. All electrocardiograms were interpreted by three examiners. The maximum degree of T-a wave depression was recorded in standard Lead II, although it was usually seen equally well in Leads III and aV_F. Record was also made of the existing cardiac position as determined from the augmented limb leads.

Group II.—Sixty additional patients were subsequently selected who showed evidence of moderately severe or severe pulmonary emphysema as detected by detailed pulmonary function testing at the Veterans Administration Hospital. Accordingly, these patients were surveyed from the electrocardiographic standpoint for the degree of existing P-wave amplitude and duration,

TABLE I. EMPHYSEMA PULMONARY FUNCTION DATA

TEST	MINIMAL	MODERATE	SEVERE
Vital Capacity	100 ± 15%	100 ± 15%	< 100%
Timed Vital Capacity 2nd Second	80 – 90%	70 – 80%	< 70%
M.B.C. (E)—Performed at Hyperinflation Level	90 – 100%(E)	70 – 90%(E)	< 70%(E)
Single Breath O_2 Test: 500 c.c.	2% N_2	2 – 4% N_2	> 4% N_2
Index Intrapulmonary Mixing	< 2.5%	2.5 – 3.5%	> 3.5%
R.V./T.L.C. × 100	20 – 30%	30 – 40%	> 40%

TABLE II. ROENTGEN SIGNS UTILIZED IN THE DIAGNOSIS OF PULMONARY EMPHYSEMA

I. Signs Due to Increase in Thoracic Volume:
   1. Depression and flattening of diaphragm
   2. Increased anteroposterior thoracic diameter, often associated with increased dorsal kyphosis
   3. Elevation of the sternum with increase in angulation between manubrium and body
   4. Widening of the intercostal spaces

II. Signs Due to Alterations in Pulmonary Parenchyma:
   1. General increase in radiolucency of lung fields along with local emphysematous bleb and bulla formation, usually at the bases or apices
   2. Superior retrosternal radiolucency increased in lateral projection
   3. Increase in interstitial markings resulting from increased contrast between hyperaerated alveoli and supporting structures (Interstitial fibrosis is also a factor in some cases)

III. Cardiovascular Changes:
   1. Decrease in peripheral vascular markings per unit area
   2. Vertical cardiac position
   3. Enlargement of pulmonary artery in severe emphysema

and T-a wave depression, and from the chest roentgenogram for the presence or absence of pulmonary emphysema. The films were so selected that the radiologist was not aware that he was reviewing a known group of emphysematous patients.

Group III.—Following completion of the above data, 1,228 routine electrocardiograms were surveyed at the Heart Station, University Hospitals, Madison, Wisconsin. The purpose of this ancillary study was threefold: (1) to determine if significant pulmonary emphysema could be detected merely by interpretation of the existing degree of T-a wave depression, (2) to determine the mean P-wave amplitude in a large, adult population, and (3) to evaluate T-a wave configuration in patients with diagnoses other than primary pulmonary diseases.

Sixty-nine patients were selected from the total series who showed T-a wave depression of 0.5 mm. or more in standard Lead II, irrespective of cardiac rate or patient age. The only group omitted were those with known congenital and acquired heart disease.

RESULTS

Group I.—Table III shows that of the 133 patients selected with T-a wave depression of 0.5 mm. or greater, irrespective of cardiac rate, 109 patients had a heart rate of 100 per minute or less. Of these 109 patients, 98 had moderate or severe pulmonary emphysema. The mean T-a wave depression was 0.75 mm. Above a cardiac rate of 100 per minute, 15 of 24 patients had gross emphysema. The mean T-a wave depression in this group was 1.18 mm. Thus, moderate or severe pulmonary emphysema was detected in 113 of the original series of 133 patients, irrespective of heart rate. The degree of T-a wave depression in this group of patients is shown in Table IV. Twenty patients with exaggerated T-a

TABLE III. GROUP I: 133 PATIENTS WITH T-A WAVE DEPRESSION OF 0.5 MM. OR GREATER

CARDIAC RATE	TOTAL NUMBER OF PATIENTS	NUMBER OF PATIENTS WITH EMPHYSEMA (MODERATE OR SEVERE)	NUMBER OF PATIENTS WITHOUT EMPHYSEMA
< 100/Min.	109	98	11*
> 100/Min.	24	15	9**

*Three patients had roentgen changes suggesting severe pulmonary emphysema, yet pulmonary function studies were borderline-normal.

**Four patients showed no significant T-a wave depression when cardiac rate fell below 90/min.

TABLE IV. GROUP I: DEGREE OF T-A WAVE DEPRESSION IN 113 PATIENTS WITH GROSS EMPHYSEMA

CARDIAC RATE	DEGREE OF T-a WAVE DEPRESSION			TOTAL
	0.5 MM.	0.75 MM.	1.0 MM. OR GREATER	
< 100/Min.	2	43	53	98
> 100/Min.	0	2	13	15

waves had no evidence of emphysema. Ten were below 30 years of age, and had moderate degrees of sinus tachycardia. In 4 of these patients, the T-a wave disappeared when the cardiac rate fell below 90 per minute. This group depicts the major pitfall in T-a wave interpretation, for apparently in young adults with minor degrees of tachycardia other factors are in operation in the production of T-a wave depression.

Of considerable interest was the finding that the roentgenographic interpretation of existing emphysema correlated with the pulmonary function data in 82 instances where both were available (94 per cent accuracy). In 8 additional instances, autopsy confirmed the roentgen impression of advanced pulmonary emphysema where pulmonary function data were not available. Disagreement of pulmonary function data and roentgen interpretation arose in only 8 instances. In 5, it was considered that the roentgenograms had been overinterpreted, and in 3, there was unequivocal roentgen evidence of severe emphysema, yet borderline-normal pulmonary function data were found.

The mean P-wave amplitudes, according to heart rate, are shown in Table V. There was no appreciable difference in mean values below a heart rate of 100/min.

Ninety-nine of the 113 patients with proved pulmonary emphysema had electrocardiographic evidence of vertical cardiac position.

TABLE V. GROUP I: MEAN P-WAVE AMPLITUDE OF 113 EMPHYSEMATOUS PATIENTS

CARDIAC RATE	NUMBER OF PATIENTS	P-WAVE AMPLITUDE (MEAN)
60–70	5	2.00
75	4	1.90
80	15	2.19
85	19	2.21
90	19	1.92
95	22	2.16
100	13	2.11
105–125	16	2.53

TABLE VI. GROUP II: 60 PATIENTS WITH KNOWN PULMONARY EMPHYSEMA

CARDIAC RATE	NUMBER OF PATIENTS	DEGREE OF EXISTING T-a WAVE DEPRESSION					X-RAY CORRELATION
		0.0-0.25 MM.	0.5 MM.	0.75 MM.	1.0 MM.	SHORT P-R: ↓ R-ST SEGMENT	
< 100/Min.	49	8*	4	28	4	5	47
> 100/Min.	11	1**	0	4	4	2	11

*Five patients had a cardiac rate of 65/min. or less—two had diminutive QRS complexes in standard Lead II (3 mm.) and one had an ectopic auricular pacemaker.

**Bizarre P-wave notching.

The T-a wave and its expression on the succeeding R-ST segment is shown in Fig. 1. Figs. 2 to 6 are representative examples of T-a waves with observed pulmonary function data and roentgenographic interpretation.

Group II.—Table VI summarizes the data on the 60 patients with clinically established moderately severe or severe pulmonary emphysema as selected by pulmonary function survey.

Thirty-two of the 49 patients with a heart rate of 100 per minute or less showed T-a wave depression in standard Lead II of 0.75 mm. or more. Eight of 11 patients showed similar findings above a heart rate of 100 per minute. Nine patients had T-a wave depression of 0.25 mm. or less, irrespective of cardiac rate. Of these 9 patients, 5 had a cardiac rate of 65 per minute or less, with diminutive P waves, 2 had diminutive QRS complexes in standard Lead II (3 mm.), 1 had an ectopic auricular pacemaker, and 1, bizarre P-wave notching.

Of real interest was the finding of 7 instances of a short P-R interval (0.12 second or less), and resultant gross depression of the succeeding R-ST segment in Leads II, III, and aV_F. This observation supports the fact that the T-a wave exerts its electromotive potential throughout the QRS complex phase, extending into the R-ST segment repolarization process. The presence of the short P-R interval deters identification of the T-a wave proximal to the QRS complex. This is shown in Fig. 7.

Roentgenographic interpretation correlated with the observed pulmonary function data in 58 of the 60 patients (96.7 per cent accuracy).

The mean P-wave amplitudes were 1.65 and 2.12 mm., respectively, for the cardiac rates below and above 100 per minute. Forty-eight of the 60 patients had vertically placed hearts.

Group III.—Table VII summarizes the data on the 1,228 patients selected for study at the University Hospitals. Of the 69 patients with T-a wave depression of 0.5 mm. or greater in standard Lead II, 34 were found to have moderate or severe pulmonary emphysema on radiographic survey. Ten of 11 patients with T-a wave depression of 1.0 mm. or more, at a heart rate of 100 per minute or less, had gross emphysema, as did 7 of 10 patients with similar T-a wave depression above a cardiac rate of 100 per minute. Five of 6 patients with the short

TABLE VII. GROUP III: 69 PATIENTS STUDIED AT UNIVERSITY HOSPITALS

CARDIAC RATE	NUMBER OF PATIENTS	DEGREE OF EXISTING T-a WAVE DEPRESSION				MODERATE OR SEVERE EMPHYSEMA ON X-RAY
		0.5 MM.	0.75 MM.	1.0 MM. OR MORE	SHORT P-R: ↓ R-ST SEGMENT	
< 100/Min.	46	18	15*	11	5	23
> 100/Min.	23	4	8	10	1	11

*One patient had heretofore undetected mitral stenosis.

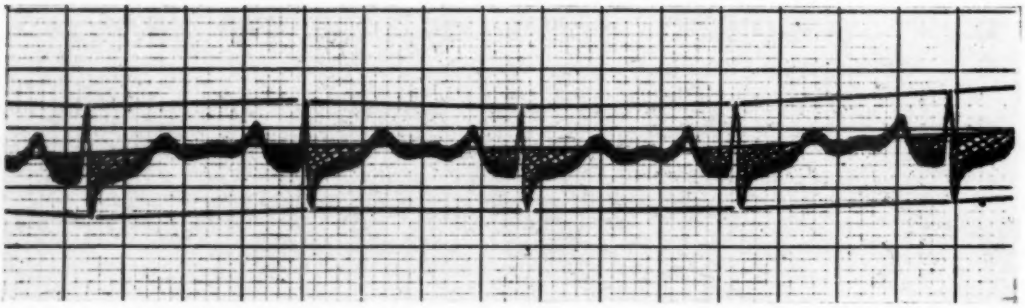

Fig. 1.—Standard Lead II. Rate 85. Patient P. L., aged 63 years—chronic cor pulmonale; no pulmonary function available due to severe respiratory embarrassment; x-ray = severe pulmonary emphysema. Prominent T-a waves are shown in the shaded areas involving the proximal P-R interval (P-Ta segment), and the succeeding R-ST segment.

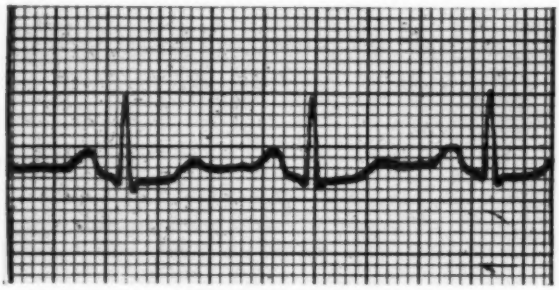

Fig. 2.—Standard Lead II. Rate 80. Patient C.P., aged 52 years.
Vital capacity 114%
Timed vital capacity: 2nd sec. 64%
Maximum breathing capacity 73% (E)
Single breath O_2 test:
500 c.c. = 2% N_2
Terminal rise 6.5% N_2
X-ray = severe emphysema

Classical T-a waves with P-wave amplitude of only 1.5 mm. and a heart rate of 80 to 85/min. The fallacy of the vital capacity in the detection of emphysematous change is evident. Although the second of the timed vital capacity was greatly reduced to 64 per cent, the total vital capacity was normal.

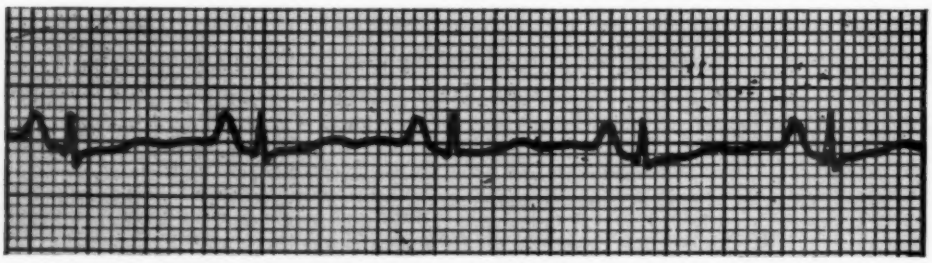

Fig. 3.—Standard Lead II. Rate 90. Patient C.W., aged 60 years.
Vital capacity 102%
Timed vital capacity: 2nd sec. 29%
Maximum breathing capacity 30% (E)
Single breath O_2 test:
500 c.c. = 10% N_2
Terminal rise 11% N_2
X-ray = severe emphysema

Prominent P waves and T-a waves with diminutive QRS complexes. Again, note the normal total vital capacity determination.

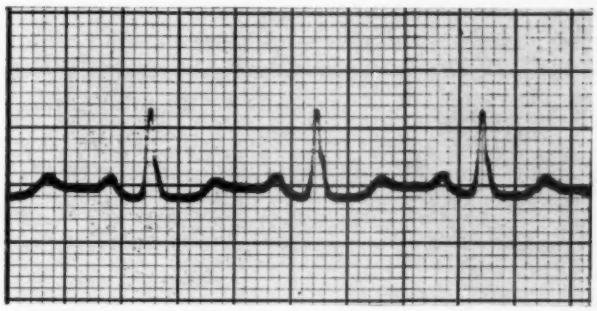

Fig. 4.—Standard Lead II. Rate 100. Patient G.B., aged 62 years.
Vital capacity 78%
Timed vital capacity: 2nd sec. 54%
Maximum breathing capacity 50% (E)
Single breath O_2 test:
500 c.c. = 9% N_2
Terminal rise 10% N_2
X-ray = severe emphysema
Prominent T-a waves without P-wave amplification.

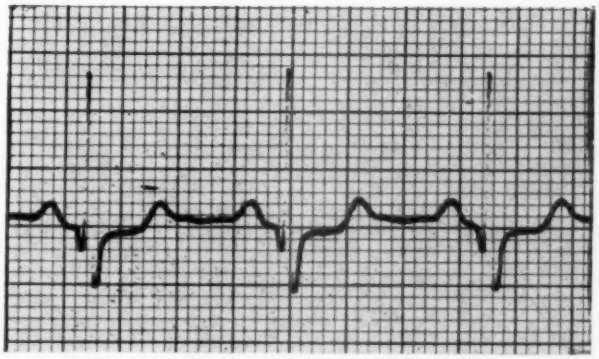

Fig. 5.—Standard Lead II. Rate 80-85. Patient T.K., aged 64 years.
Vital capacity 70%
Timed vital capacity: 2nd sec. 52%
Maximum breathing capacity 38% (E)
Single breath O_2 test:
500 c.c. = 11% N_2
X-ray = severe emphysema
Classical T-a waves with a cardiac rate of 80-85.

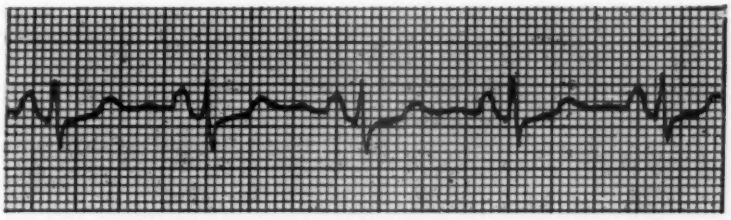

Fig. 6.—Standard Lead II. Rate 85. Patient J.B., aged 63 years.
Vital capacity 50%
Timed vital capacity: 2nd sec. 42%
Maximum breathing capacity 35% (E)
Index intrapulmonary mixing 6%
R.V./T.L.C. × 100 = 53%
X-ray = severe emphysema
Single breath O_2 test:
500 c.c. = 10% N_2
Terminal rise 16% N_2
Prominent T-a waves with prominent, but not exaggerated, P waves.

P-R interval and depressed R-ST segment pattern, irrespective of cardiac rate, had gross emphysema. Eight additional patients had minimal, but definite, emphysema on chest roentgenogram. However, because of the lack of laboratory verification, they were considered equivocal and were classified as missed cases.

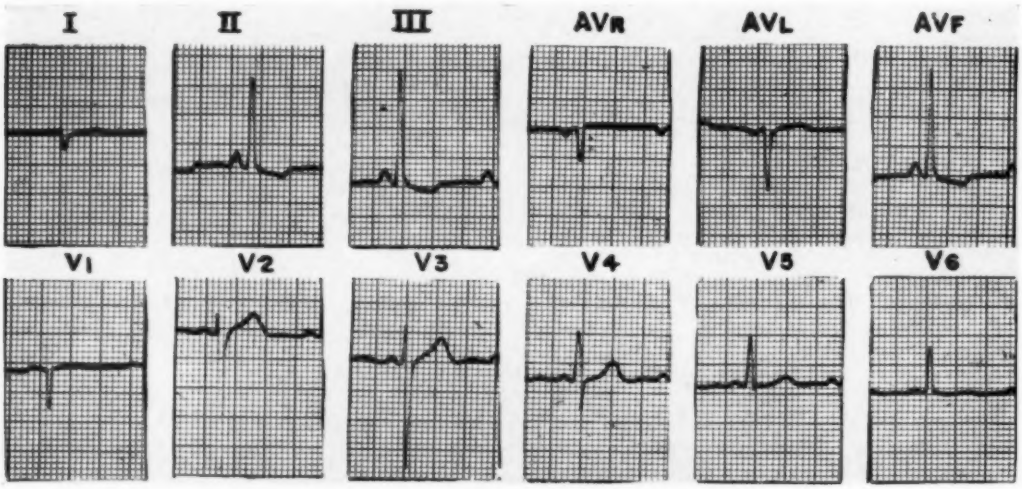

Fig. 7.—Patient W.S., aged 62 years. Cardiac rate 85-90.
Vital capacity 75%
Timed vital capacity: 2nd sec. 46%
Maximum breathing capacity 75% (E)
Single breath O_2 test:
500 c.c. = 6% N_2
Terminal rise 13% N_2
X-ray = severe emphysema
Short P-R interval, depressed R-ST segments in Leads II, III, and aV_F, with vertical cardiac position.

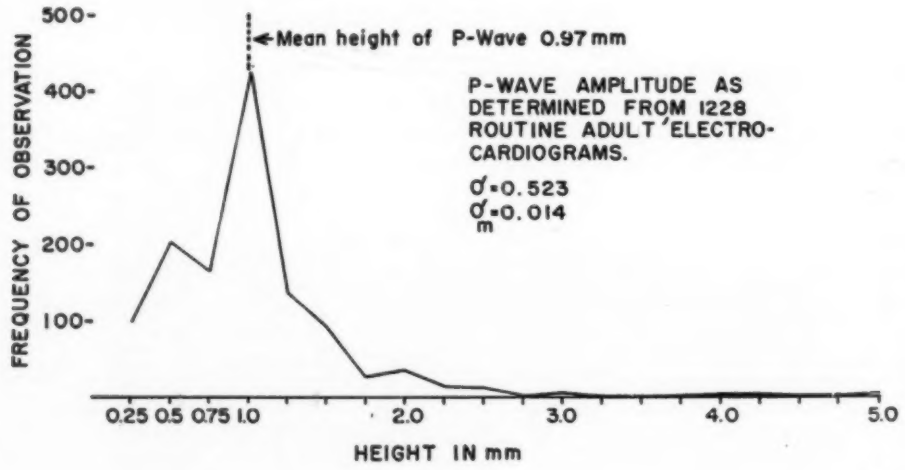

Fig. 8.

Fig. 8 depicts the curve for P-wave amplitude in standard Lead II of the entire series of 1,228 patients. Almost inclusively, all patients with prominent T-a waves were selected from the right-hand side of the curve, where the P-wave amplitude was 1.5 mm. or greater. The mean value was 0.97 mm., which is in

accord with, but slightly less than, that found in previous studies. This suggests that the average P-wave amplitude in adults is in the range of 1.0 mm. This is in sharp contrast to the selected study group of 69 patients where the mean P-wave amplitudes were 1.70 mm. below a cardiac rate of 100 per minute and 1.86 mm. above 100 per minute, and to the mean P-wave values in the patients of Group I and II with proved emphysema.

Twenty-eight of the 34 patients with gross emphysema had vertical cardiac placement.

DISCUSSION

The present study was divided into 3 separate groups of patients in order to show the relationship of prominent P waves and exaggerated T-a waves to pulmonary emphysema.

It became apparent that there were an inordinant number of patients with advanced emphysema in the Group I study, giving rise to a weighted clinical protocol. This finding arose because of the prevalence of severe emphysematous disease in the tuberculous patients hospitalized at the Veterans Administration Hospital. Accordingly, Group III was established so as to select at random patients with exaggerated T-a waves on routine electrocardiographic study, patients in whom the over-all incidence of pulmonary disease, and more specifically, gross pulmonary emphysema, was admittedly low. Nonetheless, it was found that significant pulmonary emphysema could be detected with considerable accuracy merely by correlating the degree of T-a wave depression with the cardiac rate.

Group II was designed to determine the degree of P-wave amplitude and T-a wave depression present in a selected group of patients with known, moderately severe to severe pulmonary emphysema.

The composite results of these 3 study groups appear to offer multifaceted evidence that clinically evident pulmonary emphysema does alter the repolarization pattern of auricular muscle. This is borne out by the consistently increased mean P-wave amplitude and exaggerated T-a wave depression in emphysematous patients, as compared to the accepted normal value, found in our present series of nonemphysematous patients as well as in previous studies.[1-3, 7-11] The mechanism for this electromotive phenomenon remains unanswered. One can only question the role of incipient auricular dilatation,[3] hypertrophy,[4] or injury[12,13] which is not readily identifiable by routine methods of study. Certainly there does not appear to be a significant increase in mean auricular pressure, as determined by cardiac catheterization, to suggest auricular hypertension.[11, 14-16] It is admitted, however, that the right auricle may greatly dilate before significant elevation of auricular pressure is demonstrated. Others[3,14,17] feel that the changes in the P-wave configuration seen in patients with chronic cor pulmonale may or may not be due to cardiac rotational factors. Wood[11] felt quite strongly that the vertical position of the heart did not contribute to P-wave amplification. The role of increased sympathetic tone resulting in P-wave amplification has been stressed by Lepeschkin,[17] and would help explain the false-positive group of patients found in the present study, namely, the young adult exhibiting minor degrees of tachycardia.

Regardless of the mechanism, however, the observation of prominent T-a waves in patients with established pulmonary emphysema appears real. This is in accord with the more limited series of Gross[1] and Zuckermann,[3] and the fairly comparable study of Wood.[11] In general, the degree of T-a wave depression correlated with the P-wave amplitude. However, contrary to the report of Gross,[1] in which he stated that the P-wave amplitude was directly related to an increasing cardiac rate, there did not appear to be a significant relationship between the P-wave amplitude and the cardiac rate in the emphysematous group as long as the cardiac rate remained below 100 per minute. Certainly the majority of patients in the Group I study had a heart rate between 70 and 95 per minute (Table V), yet exaggerated T-a waves were readily apparent. It was noted also that T-a wave depression of 0.75 mm. or more occurred in the emphysematous group when the P-wave amplitude was less than 2.0 mm.

Most standard texts on electrocardiography offer a value of 2.5 mm. as the upper limits of normal for P-wave amplitude in standard Lead II. From the current study of almost 3,000 adult electrocardiograms, the P wave was found to be increased above 2.5 mm. in only scattered instances, usually being associated with a sinus tachycardia. This observation suggests that only rarely does the P wave exceed 2.0 to 2.5 mm. in standard Lead II of the normal adult electrocardiogram, except for instances of gross tachycardia. Admittedly, the mean P-wave amplitude value of 0.97 mm. found in the Group III study was not completed on a truly normal adult population, inasmuch as all patients were hospitalized; however, the observed value does correlate well with previously established mean P-wave amplitudes.

The composite data of the present study bears out the following pertinent observations: (1) T-a wave depression of 0.75 mm. or more in standard Lead II of the adult electrocardiogram, below a cardiac rate of 100 per minute and with vertical cardiac position, is highly suggestive of advanced pulmonary emphysema, as is T-a wave depression of 1.0 mm. or more for a heart rate of 100 to 115 per minute. (2) The electrocardiographic pattern of the short P-R interval and depressed R-ST segment in Leads II, III and aV_F likewise suggests the presence of advanced pulmonary emphysema, inasmuch as 12 of 13 patients with this configuration had such an entity. The mechanism for this pattern is believed to be due to late expression of the T-a wave upon the succeeding R-ST segment. (3) The roentgenographic interpretation of pulmonary emphysema and its correlation with observed pulmonary function data is highly accurate, provided the criteria for selection are rigid enough to exclude the false-positive group.

The major pitfall in the interpretation of T-a wave depression appears to be in the young adult who shows minor degrees of tachycardia, and in those patients who have a gross tachycardia, i.e., 115 per minute or more, in which the T-a waves are consistently exaggerated. The role of increased sympathetic tone with varying degrees of tachycardia has been postulated previously as the probable mechanism in the production of the augmented P-wave amplitude.[18] It has been suggested also that the auricular recovery period (T-a wave) shortens with tachycardia, thereby deepening the T-a inscription.[19] This latter observation readily explains most of the false-positive examples.

The detection of exaggerated T-a wave depression and resultant R-ST segment changes has expression in disease evaluation beyond that of pulmonary emphysema. Since some degree of tachycardia attends the various exercise tests utilized in assessing coronary insufficiency, one must acknowledge the degree of T-a wave depression in the interpretation of this procedure.[19,20] Failure to appreciate the R-ST segment changes as an expression of exaggerated T-a waves may readily lead to erroneous implication of coronary artery disease.

SUMMARY

1. It appears that clinically evident pulmonary emphysema may alter the auricular repolarization pattern. This is expressed as increased P-wave amplitude and exaggerated T-a wave depression, as seen in standard Lead II of the adult electrocardiogram. This increase in mean P-wave amplitude is independent of the cardiac rate until one approaches the value of 100 per minute.

2. T-a wave depression of 0.75 mm. or greater, vertical cardiac placement, and a cardiac rate of 100 per minute or less is highly suggestive of advanced pulmonary emphysema.

3. T-a wave depression of 1.0 mm. or more with vertical position, and a heart rate between 100 and 115 per minute has similar implications.

4. The electrocardiographic pattern of a short P-R interval (0.12 second or less) and resultant gross depression of the succeeding R-ST segment in the vertically placed heart is offered as an additional expression of pulmonary emphysema.

5. Roentgenographic analysis of existing pulmonary emphysema is highly accurate, and correlates with observed pulmonary function data.

6. It is felt that pulmonary emphysema, exclusive of chronic cor pulmonale, merits additional recognition as a frequent factor in the production of prominent P waves as seen on routine electrocardiographic survey.

7. Possible mechanism in the production and pitfalls in the interpretation of T-a waves are discussed.

ADDENDUM

Since completion of this manuscript, 25 additional patients with advanced pulmonary emphysema have been studied via electrocardiography, pulmonary function testing, and chest roentgenography. T-a wave depression of 0.75 mm. or more (standard Lead II) was found in 20 instances, regardless of cardiac rate. There were 2 instances of the short P-R interval, depressed R-ST segment pattern in Leads II-III, aV_F. The 3 remaining patients had cardiac rates of 65, 70, and 90 per minute, respectively, yet none showed T-a wave depression of 0.5 mm. and were classified as missed cases. Correlation of emphysema by pulmonary function testing and chest roentgenographic interpretation again was most consistent. There were 2 instances of severe pulmonary emphysema on pulmonary function studies, yet roentgenographic interpretation was that of only minimal change.

One additional sign which is invaluable in assessing the significance of a given T-a wave, providing the previously described criteria are in evidence, is the finding of low voltage (5 to 8 mm.) in the left ventricular leads, with or without moderate degrees of clockwise rotation. This serves to separate the "false positive," seen in young adults with mild degree of tachycardia, i.e., 90 to 110.

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THE COMPARATIVE POTENCY OF MERCURIAL DIURETICS USING HUMAN BIO-ASSAY TECHNIQUES

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EXPERIENCES with the determination of comparative potency of diuretic agents have emphasized the need for controlled studies. The most important variable would appear to be the sodium and water load of the subject patient. If such factors could be controlled, the response to a given diuretic would be dependent on the dose of that diuretic and its specific potency. The testing of this hypothesis is the substance of this report.

METHODS AND MATERIALS

The subject for the first study was a 29-year-old male laboratory technician who was hospitalized for a period of 6 months because of minimal tuberculous lymphadenitis. He was afebrile and clinically free of symptoms throughout the study. He was maintained in an air-conditioned metabolic ward and was allowed to be ambulatory about the ward. He was fed weighed diets which had a constant caloric content (2,900 calories per day) consisting of 400 Gm. carbohydrate, 100 Gm. protein, and 100 Gm. fat. He also drank 3,000 ml. of distilled water per day. During the first 3 months the diet contained 150 meq. of sodium per day, and during the second 3 months it contained 50 meq. The patient was weighed each morning before breakfast and after voiding. After 10 days the excretion rate of sodium per 24 hours varied less than 10 per cent. Initially, diglucomethoxane (Mersoben) was given by the intramuscular route in a dose equivalent to 20 mg. of mercury. Subsequent doses of 40 and 80 mg. of mercury equivalent were given.† Each dose was repeated at least 3 times consecutively and again in a round of progressively increasing doses. Before each subsequent dose of the diuretic was administered, the patient had returned to his control state for at least 72 hours with respect to weight and excretion of water and electrolytes. This same procedure was repeated while the patient was eating the second diet, which contained only 50 meq. of sodium. Urine was collected for 24-hour periods in Pyrex bottles. Analyses of sodium and potassium content in the urine were done using a Beckman flame photometer (Model DU); chloride was analyzed by the modified method of Sendroy‡; and creatinine, as a test of the completeness of the 24-hour collection, was analyzed by the method of Folin.§ Blood electrolytes, including sodium, potassium, chloride, and carbon dioxide content, and hematocrit were determined at intervals to ascertain their constancy.

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†A single injection of 160 mg. of mercury equivalent was given but was not repeated because of diarrhea and muscular cramps.

‡Method of Sendroy modified by Van Slyke and Heller.[2]

§Folin's method. (Ref. 2, p. 893).

In the second study, 12 males who had recovered from congestive heart failure were observed. At the time of the study, there was no detectable edema, indicating that these individuals were roughly similar in the degree of heart failure present. The patients were maintained on an air-conditioned metabolic ward under the observation of trained personnel. Digitalis, if previously required for the control of their heart disease, was continued throughout the study. The patients were allowed to be ambulatory about the ward. The diet consisted of 300 Gm. of carbohydrate, 100 Gm. of protein, and 100 Gm. of fat, with a total of 2,500 calories per day. The sodium content of the diet for each patient was constant, but varied between patients from 35 to 350 meq. per 24 hours. The patients drank 3,000 ml. of distilled water per day. They were allowed to equilibrate on this diet until they excreted a constant quantity of sodium, which approximated 90 per cent of the dietary sodium intake. The diuretic agent to be tested was then administered. Several days were then allowed for the patient to regain his body weight by the restoration of sodium and water stores before the next dose of the diuretic to be tested was administered. The patients were weighed before breakfast and after voiding each morning. Urine was collected in 24-hour periods and analyses were conducted as mentioned above. The data has been subjected to an analysis of variance.[1]

RESULTS

I. *The Influence of Dietary Sodium on the Response to a Mercurial Diuretic.*—There was a progressive increase in the response to increasing doses of diglucomethoxane (Mersoben), with control levels of excretion being quite constant (Table I). The increase in the excretion rates of sodium and chloride were largest. Weight and water changes were at a lower level. There was an insignificant change in the potassium excretion. The effect of the dietary levels of sodium (150 and 50 meq. per day) also was reflected in the degree of response in

TABLE I. THE EFFECT OF VARIOUS DOSES OF DIGLUCOMETHOXANE (MERSOBEN), ADMINISTERED AT TWO DIETARY SODIUM LEVELS, ON BODY WEIGHT AND EXCRETION OF WATER AND ELECTROLYTES

	DOSAGES OF MERSOBEN		
	20 MG. Hg I ± S.E.	40 MG. Hg I ± S.E.	80 MG. Hg I ± S.E.
	Diet I: 150 meq. Sodium		
Sodium	71 ± 14	115 ± 14	272 ± 17
Chloride	68 ± 16	119 ± 16	258 ± 18
Water	0.42 ± 0.13	0.36 ± 0.13	1.17 ± 0.16
Weight	− 0.2 ± 0.15	−0.6 ± 0.15	−1.5 ± 0.17
Potassium	−17 ± 6	−8 ± 7	−7 ± 7
	Diet II: 50 meq. Sodium		
Sodium	14 ± 17	78 ± 14	149 ± 14
Chloride	15 ± 18	91 ± 16	195 ± 16
Water	0.03 ± 0.16	0.21 ± 0.13	0.44 ± 0.13
Weight	0.1 ± 0.17	−0.1 ± 0.15	−0.4 ± 0.15
Potassium	−15 ± 7	−18 ± 6	1 ± 6

Electrolytes are expressed as meq./24 hours; weight as Kg./24 hours; water as L./24 hours. I = Mean increase ± Standard Error.

each of the excretory factors except potassium. In order to convert these data into a concept of the effect of sodium intake on the diuretic response to the mercurial, dosage response curves were constructed, comparing the two diets (150 and 50 meq. sodium content). In Fig. 1, the top line represents the dosage response curve for sodium excretion obtained when the patient was eating a diet containing 150 meq. of sodium, while the lower line represents the curve at 50 meq. of dietary sodium. The vertical dotted line illustrates the range of variation at each level (standard error or confidence limits). In all moieties (sodium, chloride, water, and weight) and in all dosages of the drug (20, 40, and 80) the response was greater when the dietary sodium was greater.

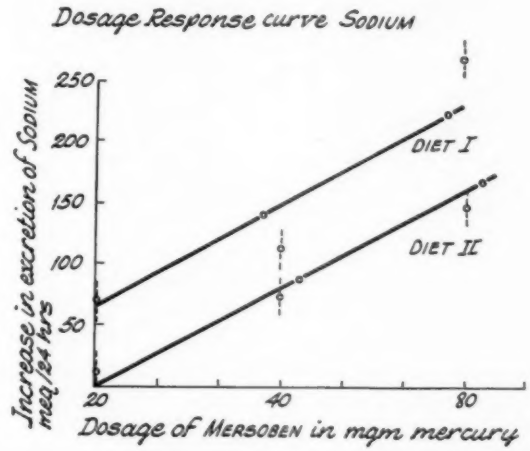

Fig. 1.—Dosage response curve for sodium excretion due to diglucomethoxane (Mersoben) in a patient receiving two dietary sodium loads. Diet I contains 150 meq. of sodium. Diet II contains 50 meq. of sodium.

II. *The Comparative Potency of Various Diuretics.*—The basic data from studies on patients with cardiac disease are presented in tabular form. The observations indicated that there was a progressive increase in the response to each increasing dose of a given diuretic, and there was a difference in response when the various agents were compared.

The average changes in sodium, chloride, potassium and water excretion and weight loss along with the standard errors are presented in Table II. The excretion rates of sodium and chloride showed the greatest response; weight and water changes were less prominent (without proportionate decrease in standard error). Potassium excretion was not affected significantly.

In order to compare further the effectiveness of the diuretic agents under study, dosage response curves were drawn (Fig. 2). In the curves representing the dosage response in sodium excretion, chlormerodrin (Neohydrin) administered parenterally demonstrates the greatest increase, followed by diglucomethoxane (Mersoben), meralluride (Mercuhydrin), mercaptomerin (Thiomerin), also given parenterally, and finally chlormerodrin (Neohydrin) given orally.

TABLE II. SUMMARY OF MEAN CHANGES DUE TO MERCURIAL DIURETICS AND THEIR STANDARD ERRORS

DRUG	DOSE MG. Hg	SODIUM $\bar{I} \pm$ S. E.	CHLORIDES $\bar{I} \pm$ S. E.	WATER $\bar{I} \pm$ S. E.	WEIGHT $\bar{I} \pm$ S. E.	POTASSIUM $\bar{I} \pm$ S. E.
Mercuhydrin	20	63 ± 33	60 ± 26	0.30 ± 0.25	0.19 ± 0.24	2 ± 6
	40	136 ± 30	83 ± 23	0.33 ± 0.22	0.50 ± 0.19	4 ± 5
	80	187 ± 28	170 ± 23	0.60 ± 0.22	0.79 ± 0.19	5 ± 5
Mersoben	20	67 ± 28	195 ± 23	0.66 ± 0.22	0.37 ± 0.19	1 ± 5
	40	194 ± 33	195 ± 28	0.70 ± 0.25	0.38 ± 0.22	−1 ± 6
	80	199 ± 28	288 ± 23	0.96 ± 0.22	0.70 ± 0.19	−3 ± 5
Neohydrin (P)	20	145 ± 33	146 ± 26	0.53 ± 0.25	0.56 ± 0.22	−19 ± 6
	40	233 ± 33	186 ± 26	1.10 ± 0.25	1.02 ± 0.22	−8 ± 6
	80	316 ± 33	251 ± 26	1.78 ± 0.25	1.36 ± 0.22	−1 ± 6
Neohydrin (O)	20	7 ± 37	42 ± 26	0.16 ± 0.28	0.23 ± 0.24	−4 ± 6
	40	76 ± 30	31 ± 24	0.24 ± 0.23	0.35 ± 0.19	−7 ± 5
	80	119 ± 31	115 ± 25	0.49 ± 0.24	0.22 ± 0.20	3 ± 5
Thiomerin	20	55 ± 33	44 ± 26	0.18 ± 0.25	0.04 ± 0.22	−15 ± 6
	40	98 ± 28	72 ± 23	0.52 ± 0.22	0.62 ± 0.19	−9 ± 5
	80	120 ± 28	113 ± 23	0.96 ± 0.22	0.61 ± 0.19	5 ± 5

Electrolytes are expressed as meq./24 hrs.; weight as Kg.; water as L./24 hrs.
$\bar{I}$ = mean change. S.E. = standard error. O = orally. P = parenterally.

TABLE III. POTENCY ESTIMATIONS OF MERCURIAL DIURETICS AS COMPARED TO A STANDARD—MERCUHYDRIN*

	THIOMERIN	NEOHYDRIN P#	NEOHYDRIN O#	MERSOBEN
Sodium	$R_U = 2.4$ $R = 0.6$ $R_L = 0.3$	$R_U = 7.8$ $R = 3.3$ $R_L = 1.8$	$R_U = 0.9$ $R = 0.5$ $R_L = 0.5$	$R_U = 2.3$ $R = 1.3$ $R_L = 0.7$
Weight	$R_U = 3.8$ $R = 0.9$ $R_L = 0.4$	$R_U = 106.4$ $R = 6.7$ $R_L = 2.3$	$R_U = 1.9$ $R = 0.7$ $R_L = 0.1$	$R_U = 6.0$ $R = 1.5$ $R_L = 0.5$
Chlorides	$R_U = 1.2$ $R = 0.7$ $R_L = 0.4$	$R_U = 7.7$ $R = 3.4$ $R_L = 1.2$	$R_U = 1.1$ $R = 0.6$ $R_L = 0.3$	$R_U = 3.4$ $R = 1.8$ $R_L = 1.1$
Water	$R_U = 4.5$ $R = 1.3$ $R_L = 0.7$	$R_U = 49.9$ $R = 6.0$ $R_L = 2.4$	$R_U = 1.8$ $R = 0.8$ $R_L = 0.3$	$R_U = 9.6$ $R = 2.6$ $R_L = 1.2$

*1 mg. of Drug II (etc.) is equivalent in action to R mg. of the standard, e.g., 1 mg. Thiomerin = 0.6 mg. Mercuhydrin as a natriuretic agent and 0.7 mg. Mercuhydrin as a chloruretic agent.

R is the best estimate of the potency of Drug II with respect to the standard, Drug I (Mercuhydrin).

R_U and R_L are upper and lower 5 per cent fiducial limits on this estimate of potency. (Calculated according to Fieller's theorem.)

P# and O# indicate the parenteral and oral forms of the drug, respectively.

Since the analysis of variance reveals that the curves are parallel and linear and that the error is not significant, one can compare mathematically the dosage response curves related to a standard drug such as meralluride (Mercuhydrin) to determine a "potency estimation." These calculations (Table III) also furnish fiducial limits of the potency estimation, which are referred to as R_U and R_L, as the upper and lower 5 per cent fiducial limits. R is the best estimate of potency of the unknown drug with respect to the standard, meralluride (Mercuhydrin).

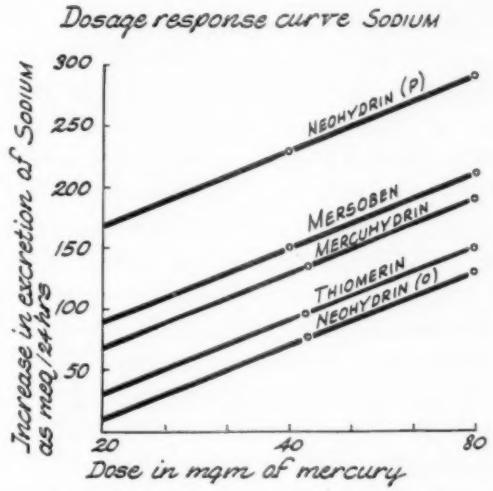

Fig. 2.—Dosage response curves for sodium excretion due to various mercurial diuretics.

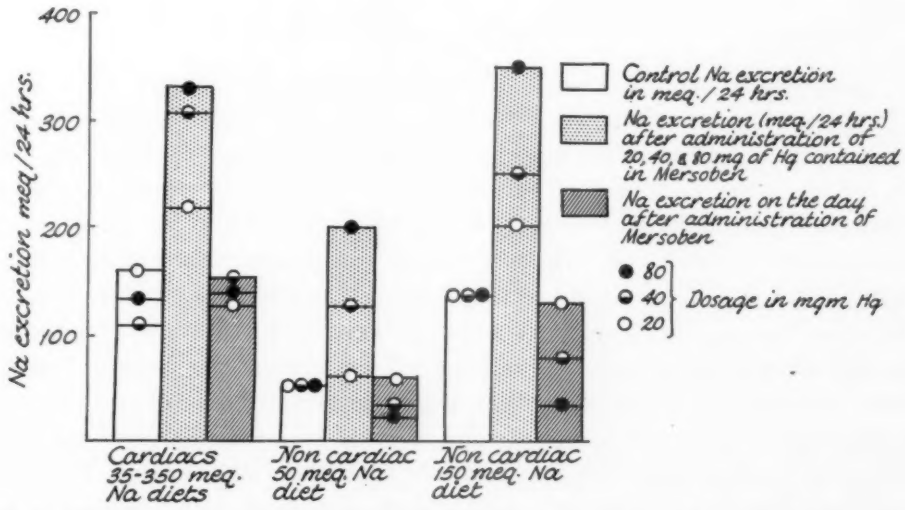
Na excretion meq./24 hrs.
400
300
200
100
Control Na excretion in meq./24 hrs.
Na excretion (meq./24 hrs.) after administration of 20, 40, & 80 mg of Hg contained in Mersoben
Na excretion on the day after administration of Mersoben
80
40
20
Dosage in mgm Hg
Cardiacs 35-350 meq. Na diets
Non cardiac 50 meq. Na diet
Non cardiac 150 meq. Na diet

Fig. 3.—These bar graphs illustrate the similarity of the response in sodium excretion to a diuretic, diglucomethoxane (Mersoben), when given to cardiac patients eating diets of varying sodium content (35 to 350 meq.) and to a noncardiac individual eating a 150 meq. sodium diet. The noncardiac, however, has a different recovery pattern (postdrug day) in that sodium excretion is depressed more markedly in order to replace the lost sodium more rapidly. It further illustrates the "potency" of an increased sodium diet in the noncardiac in potentiating the effect of the diuretic agent.

Thus, when sodium is the function studied, these calculations indicate that parenterally administered chlormerodrin (Neohydrin) is the most potent (3.3 times the potency of meralluride), followed by diglucomethoxane (Mersoben) which is 1.3 times as potent as meralluride, mercaptomerin (Thiomerin) which is 0.6 times as potent, and orally administered chlormerodrin (Neohydrin) which is 0.5 times as potent as meralluride. Furthermore, the narrow fiducial limits of this function (as well as chloride) as contrasted with those of weight and water changes indicate that the responses are more consistent. Thus, greater confidence can be placed in the assay when sodium excretion is used as the indicator of potency. During the study there was no significant clinical effect of an untoward nature or change in plasma electrolytes, electrocardiogram, urinalysis, or blood urea nitrogen which could be attributed to the drugs, except for pain after the intramuscular injection of chlormerodrin (Neohydrin).

Utilizing the data of the two studies, a comparison of the response in sodium excretion following diglucomethoxane (Mersoben) in a normal man and in the group of cardiac patients is presented in Fig. 3. When the diets were not constant in sodium content among the patients, as in the cardiac group, the average control sodium excretion was roughly similar to that of the noncardiac man eating a diet containing 150 meq. of sodium. The response to the diuretic was approximately the same on the second day after the drug was given. However, the sodium excretion was reduced to a greater degree in the normal man than in the cardiac patients. Since the control sodium excretion was similar, this may indicate that renal compensatory mechanisms for the conservation of sodium are more sensitive in the normal subject than in patients with heart failure. However, it may indicate a greater sodium load available for excretion in the cardiac which is not reflected in the total sodium excretion in the first 24 hours after the drug is administered.

DISCUSSION

In the first study of this report it was shown that the response to a diuretic agent was dependent upon the dietary sodium intake and the dose of the diuretic agent. Since these factors may be controlled, differences between drugs can be determined by utilizing controlled dietary sodium techniques. The technique consists simply in maintaining the patients to be tested on constant sodium intake (as well as water) and giving diuretic agents only as the control state approache the same as that seen previously with respect to sodium excretion. In the second study, the diets of the patients were constant within a given patient, but varied between patients. This required that a greater number of patients be tested in their responses to the various diuretic agents before the changes were significantly different. It is of interest that there was no significant difference in the response to a diuretic agent in a group of patients with controlled congestive heart failure and in a normal man.

Valuable information derived from the study is that of the potency estimations of four diuretics compared to a standard, meralluride (Mercuhydrin). It is seen that chlormerodrin (Neohydrin) is the most potent drug when administered

parenterally (however, it is not commercially available), followed by diglucomethoxane (Mersoben), both of which are more potent than meralluride (Mercuhydrin). Orally administered chlormerodrin (Neohydrin) and parenterally administered mercaptomerin (Thiomerin) are less potent.

SUMMARY

1. The factors influencing the response to a mercurial diuretic have been studied in a patient without congestive heart failure under metabolically controlled conditions. The responses of the excretion rate of sodium, chloride, and water and the change in weight are distinctly dependent upon dietary sodium. The response to a single diuretic agent, diglucomethoxane (Mersoben), is also distinctly dependent on dose.

2. By use of the analysis of variance, the computation of potency estimation, with its fiducial limits for each response observed, is possible. Statistical efficiency is improved when the potency estimation is calculated from the responses in sodium (or chloride) excretion rather than from the responses in weight change.

3. Thus, in order to evaluate satisfactorily the comparative potency of the various diuretic agents, the patients must receive an identical sodium content diet and have the same water load (they need not be in congestive failure), and the observations should include the excretion of sodium (or chloride).

4. The potency estimations of the various drugs when related to meralluride (Mercuhydrin) as the standard drug, using sodium as the function tested, were as follows: parenteral chlormerodrin (Neohydrin), 3.3; diglucomethoxane (Mersoben), 1.3; mercaptomerin (Thiomerin), 0.6; and oral chlormerodrin (Neohydrin), 0.5.

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THE EFFECT OF SEDATION ON THE ABNORMAL BALLISTOCARDIOGRAM OF FATIGUE

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THE high incidence of abnormal ballistocardiograms in otherwise healthy individuals has long been recognized as a problem in the development of this method of cardiovascular evaluation. The increasing incidence with age of abnormal ballistocardiograms suggested that the ballistocardiogram is a sensitive indication of preclinical coronary artery disease.[1,2] And indeed, as Starr has shown, an abnormal ballistocardiogram may be the forerunner of other signs of arteriosclerotic heart disease. Evidence has gradually been accumulated, however, that some of these ballistocardiographic abnormalities are not the result of cardiac malfunction.[3-7]

Studies by Dock[8] and others[9,10] have indicated that as age advances the vector of cardiovascular force tends to become more transverse, and that a transverse ballistocardiogram, therefore, may be normal, whereas the longitudinal ballistocardiogram is abnormal. Such a change in vector direction may explain the longitudinal abnormalities in some patients with dilated and elongated aortas, but does not explain many more abnormalities in patients with normal aortas.

The important and complex nature of the influence of extracardiac factors on the ballistocardiogram has been indicated by many investigators.[11-17] External and internal body linkage systems have been defined, and an approximation of the distorting effect of the external linkage system has been calculated. These calculations have shown that the loading effect of a heavy bed or the frictional resistance between the body and a fixed surface distort the ballistocardiogram appreciably. The distorting effect of internal body linkage systems, however, is difficult to determine.

A simple demonstration of apparent change in body linkage was observed by us in several of our early experiments. These experiments kept the subject on a fixed hard surface for over an hour with a block of wood under the Achilles tendons, an ordeal occasionally resulting in the deterioration of a normal direct-

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body ballistocardiogram with no other manifest change in circulatory phenomena. Such an observation led to this investigation of the effect of fatigue and sedation on body linkage and its relation to the circulation.

METHOD

Records were obtained from 20 patients, 10 with no evidence of heart disease and 10 with heart disease. The patients were evaluated by history, physical examination, electrocardiograms, and chest roentgenograms.

Each patient was placed on a hard, fixed table top, and a block of wood was set under the Achilles tendons. This block of wood produced hyperextension of the knee joints and stretched the hamstrings, inducing considerable discomfort after a time. A bar with a coil attached was placed across the shins, and a magnet, fixed to the table, was approximated to the coil. Thus, the ballistocardiogram was recorded by the method of Dock and Taubman.[18]

Simultaneous tracings were obtained also of Lead II of the electrocardiogram, respiration, electromyogram of the flexor muscles of the forearm, and the brachial pulse with a base line pressure equal to that of the subject's diastolic pressure. These phenomena were traced on a Grass multichannel recorder. Blood pressures were recorded at intervals.

Control tracings were obtained on each patient ½ to 1 hour after he or she was placed on the table. Then tracings were recorded every 10 minutes until the ballistocardiogram had deteriorated. At this time the patient was given sodium Amytal intravenously in doses of 250 mg. One to 3 doses were required to put the patient to sleep. Tracings were repeated during sleep, and shortly after awakening.

Hypnosis was used also to put some of the patients to sleep. This procedure was performed by one of our psychiatrists. It was a useful means of producing stress in the form of pain, muscle tension, or fatigue. In several experiments, with the patient under hypnosis, the psychiatrist suggested to the patient that he would be very tired when he was awakened. A sense of fatigue could be produced rapidly by this method.

Since the abnormalities evident in the direct-body ballistocardiogram might be attributed to the distortions inherent in the external body linkage, ballistocardiograms were obtained also from an ultralow-frequency bed, such as that described by Rappaport.[19] Plastic fabric supported by an aluminum frame, weighing 4 pounds, was suspended from the ceiling by 6-foot wires. This bed had a natural resonant frequency of approximately 0.3 cycles per second. In some experiments the bed was undamped, and in others it was damped with cotton. A quarter inch plywood board, weighing 8 pounds, was placed on the aluminum frame and a bar was placed under the Achilles tendons in order to increase the discomfort of some subjects. A magnet was attached to the bed and a stationary coil placed in apposition to it. The velocity ballistocardiogram was recorded in held inspiration and held expiration. Lead II of the electrocardiogram was recorded simultaneously. Blood pressures were taken periodically. Ten of the patients upon whom direct-body ballistocardiograms had been recorded were studied also on the ultralow-frequency bed.

RESULTS

Patients from our psychosomatic service with no evidence of cardiovascular disease, ranging in age from 18 to 52 years, were used as normals. Seven of these patients had normal control ballistocardiograms, and 3 had abnormal control ballistocardiograms. For the purpose of this study, we have defined the abnormal ballistocardiogram as one which shows (1) respiratory deterioration as described by Brown,[20] or (2) marked change in the amplitude of H-I, I-J, or J-K strokes as compared to the rest of the ballistic complex, or (3) significant change in the timing of the strokes in relation to the electrocardiogram. Fatigue was induced by having the patient lie on a hard table with a block of wood under his Achilles tendons for 1½ to 3½ hours. Tracings taken at the end of this period were all

abnormal, and 4 of them had few or no recognizable ballistic complexes. It is interesting to note that the myograms of some of these patients showed more activity at the end of the fatigue period than during the control period. All of the ballistic abnormalities disappeared promptly when sleep was induced by sodium Amytal. Even those patients with abnormal control tracings had normal sodium Amytal sleep tracings. No significant blood pressure changes were noted.

Fig. 1 shows the tracings of an 18-year-old male asthmatic in remission. The tracings, taken at the end of 2 hours and 40 minutes of lying on a hard surface, show abnormality of all of the ballistic complexes except the last one. The electromyogram at this time shows some increase in muscle activity. The sodium Amytal sleep tracings show a return of the ballistocardiogram to normal and some diminution of muscle activity.

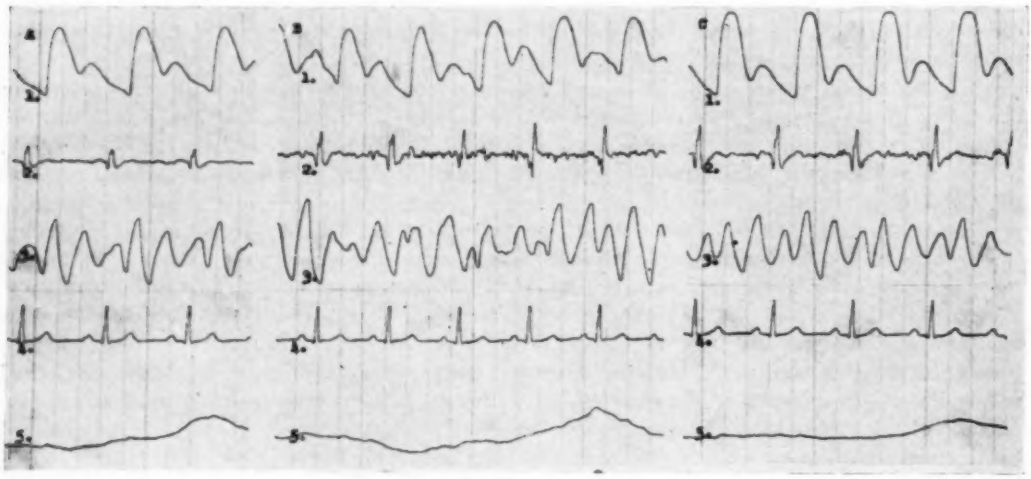

Fig. 1.—The effect of fatigue and sedation on the normal direct-body ballistocardiogram. Channel 1: brachial pulse. Channel 2: electromyogram from the forearm. Channel 3: direct-body velocity ballistocardiogram. Channel 4: Lead II of the electrocardiogram. Channel 5: respiration; inspiration is upward. Section *A* shows the control tracings. Section *B* was taken at the end of the fatigue period. Section *C* was taken after the patient was put to sleep with sodium Amytal.

Fig. 2 is taken from the tracings of a 19-year-old male with a duodenal ulcer. It shows the effect of 3½ hours of table fatigue. Ballistic complexes are present, but the H-I and I-J strokes are abnormally small, and there is some delay in their appearance. These abnormalities are absent in the tracing taken immediately after the patient was put to sleep with sodium Amytal. When discomfort is again experienced, the ballistocardiogram shows deterioration once more. The H-I and I-J strokes are abnormally small and are delayed in their appearance. The improvement in pulse amplitude during sleep might be considered to have some bearing on the change between fatigue and sedation, were it not for the fact that pulse amplitude during the reinstatement of fatigue is the same as that during sleep. This patient's electromyogram did not change significantly.

The abnormal group consisted of 10 patients, ranging in age from 42 to 72 years, with arteriosclerotic heart disease, rheumatic heart disease, thyrotoxic

heart disease, and hypertensive cardiovascular disease. These patients were all in a stable state with no evidence of heart failure. The blood pressures of the hypertensive patients had been regulated, and were all normal except one.

Nine of these patients had abnormal control ballistocardiograms, and 1 had a normal ballistocardiogram. All of the tracings except 1 became more abnormal after 1 to 2 hours of fatigue, and 3 of the tracings lost all evidence of a recognizable pattern. With sleep induced by sodium Amytal, the ballistocardiograms of all 10 patients improved; 4 became normal, including the 1 where the prefatigue tracing had been normal, and 6 returned to the prefatigue pattern.

Fig. 3 is taken from the tracings of a 42-year-old male with thyrotoxic heart disease, under antithyroid therapy. The control tracings show some diminution in amplitude of the H-I and I-J strokes with delay in their appearance. The ballistocardiogram becomes much more abnormal and irregular after 1 hour and 40 minutes of fatigue. The complexes are discernible, but vary more in amplitude and are partially obscured by many smaller oscillations of the base line. The tracings taken immediately after sleep was induced by sodium Amytal show normal ballistic complexes. The electromyogram shows less muscle activity.

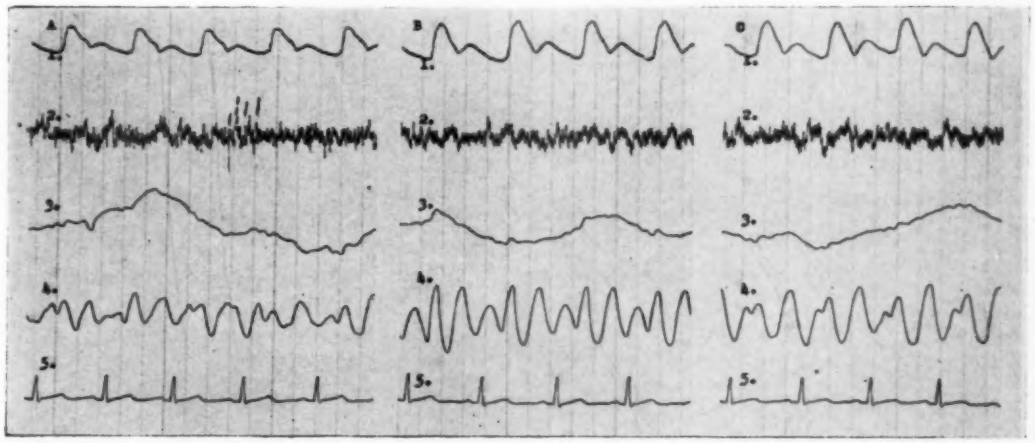

Fig. 2.—The effect of sedation on the abnormal ballistocardiogram of fatigue. Channel 1: brachial pulse. Channel 2: electromyogram from the forearm. Channel 3: respiration; inspiration is upward. Channel 4: direct-body velocity ballistocardiogram. Channel 5: Lead II of the electrocardiogram. Section *A* shows the tracings taken after 3½ hours of fatigue. Section *B* shows tracings taken during sodium Amytal induced sleep. Section *C* shows tracings taken after the patient was again awake and experiencing considerable discomfort.

Hypnosis was substituted for sodium Amytal in 2 of the patients with heart disease. The control tracing of one, a hypertensive, showed inspiratory deterioration of the ballistic pattern which became worse with fatigue, and became normal under hypnosis. The tracings from the other patient with thyrotoxic heart disease became worse under hypnosis.

To eliminate the factor of external body linkage, 10 of the 20 patients who had been tested with the direct-body ballistocardiogram were re-tested on the ultralow-frequency bed. The control tracings of 4 of the 10 patients were abnormal, and the other 6 were normal. It was found to be more difficult to induce

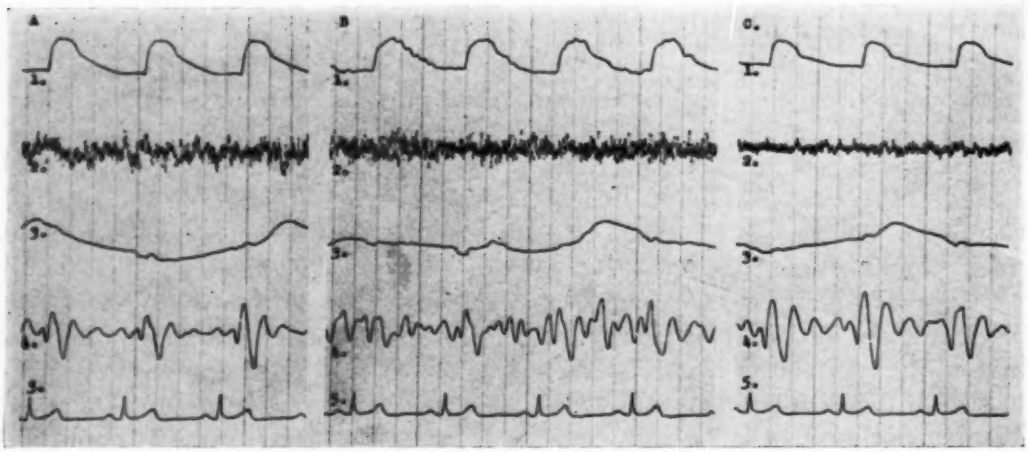

Fig. 3.—The effect of fatigue and sedation on the abnormal ballistocardiogram. Channel 1: brachial pulse. Channel 2: electromyogram from the forearm. Channel 3: respiration; inspiration is upward. Channel 4: direct-body velocity ballistocardiogram. Channel 5: Lead II of the electrocardiogram. Section *A* shows the control tracings. Section *B* shows the tracings taken after 1 hour and 40 minutes of fatigue. Section *C* shows the tracings taken immediately after sleep was induced by sodium Amytal.

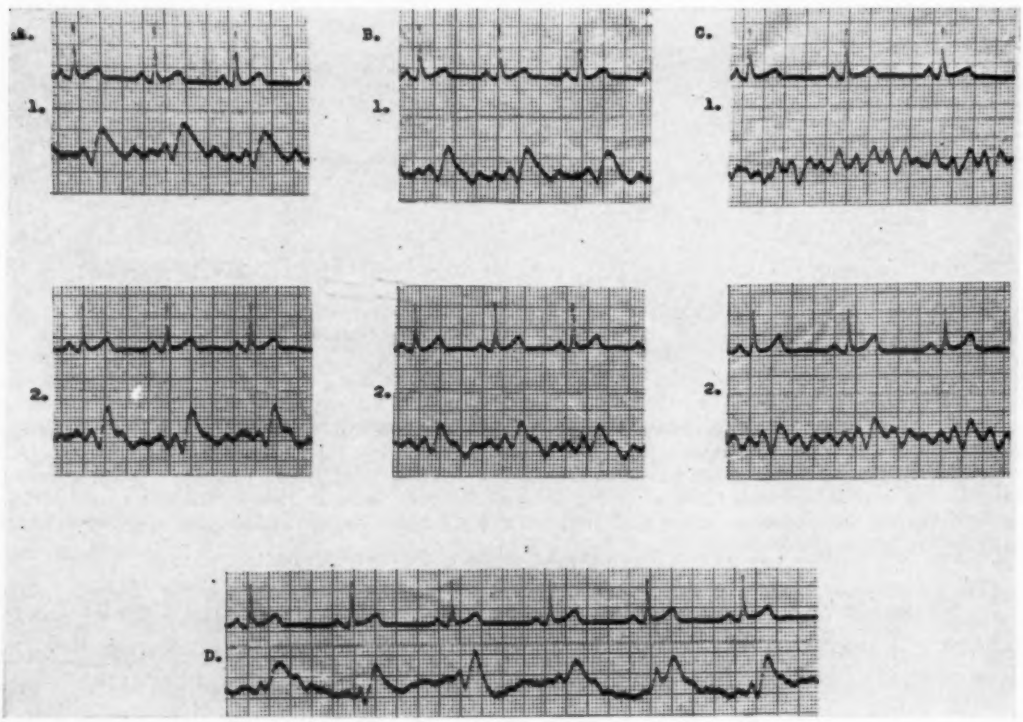

Fig. 4.—The effect of fatigue and sedation on the normal ultralow-frequency bed ballistocardiogram. Number *1* groupings show held inspiration, and Number *2* groupings show held expiration. The ballistocardiograms are timed by Lead II of the electrocardiogram. Section *A* shows the control ballistocardiograms. Section *B* shows the tracings taken with the patient relaxed under hypnosis. Section *C* shows the tracings taken when the patient awakened following the posthypnotic suggestion that he would be tired and uncomfortable. Section *D* shows the sodium Amytal induced sleep ballistocardiogram with the patient breathing quietly.

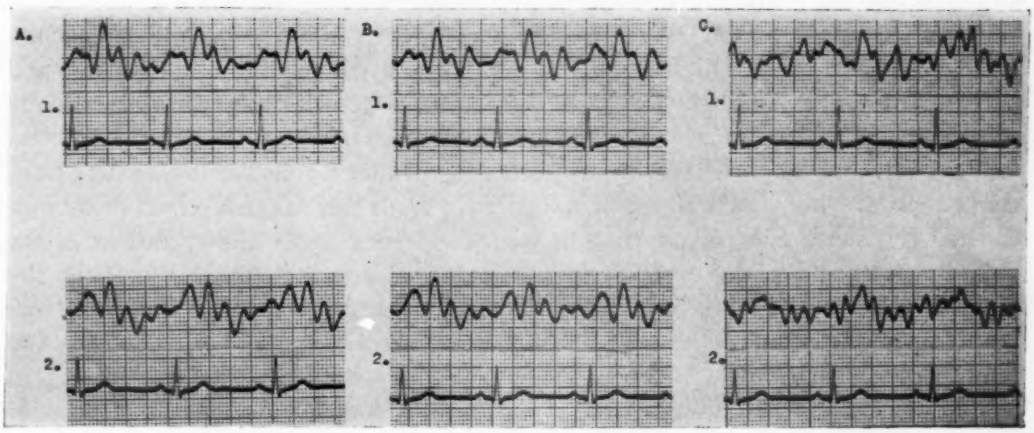

Fig. 5.—The effect of fatigue on the ultralow-frequency ballistocardiogram. Number *1* groupings show held inspiration, and Number *2* groupings show held expiration. The ballistocardiograms are timed by Lead II of the electrocardiogram. Section *A* shows the control ballistocardiogram. Section *B* shows the tracings taken with the patient relaxed under hypnosis. Section *C* shows the tracings taken during posthypnotic fatigue.

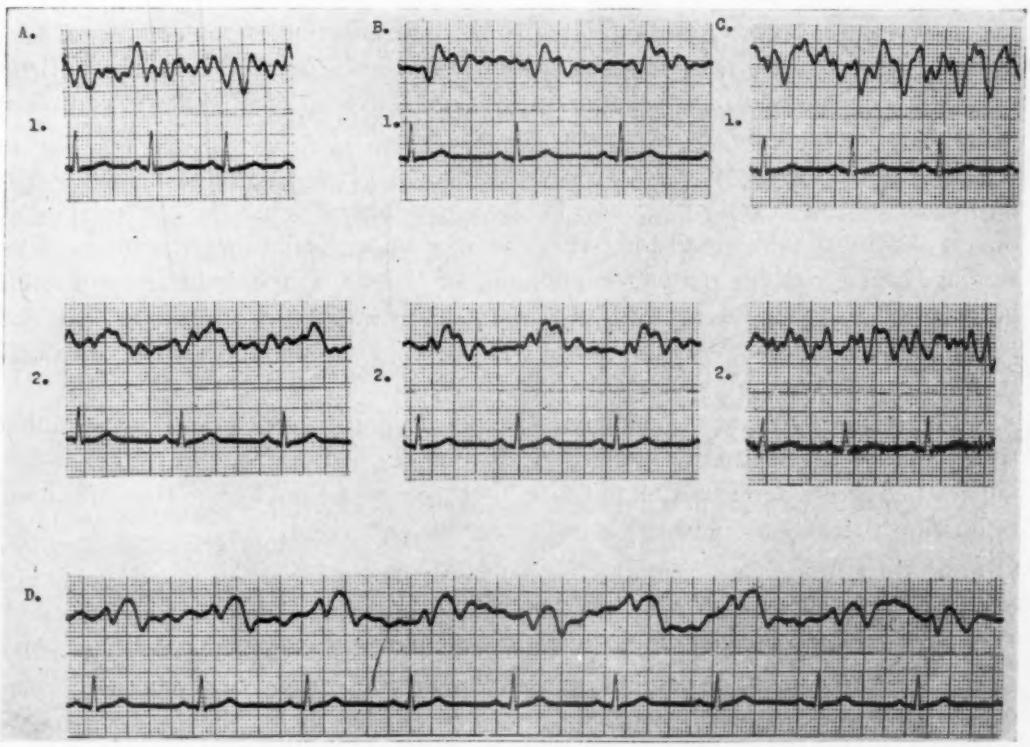

Fig. 6.—The effect of fatigue and sedation on the ultralow-frequency ballistocardiogram. Number *1* groupings show held inspiration, and Number *2* groupings show held expiration. The ballistocardiograms are timed by Lead II of the electrocardiogram. Section *A* shows the tracings taken after lying on the ultralow-frequency bed for 2 hours and 10 minutes. Section *B* shows the tracings taken immediately after awakening from sodium Amytal sleep. Section *C*, taken shortly thereafter, shows the effect of having the patient tighten his back muscles voluntarily. Section *D* shows the ballistocardiogram taken during sodium Amytal induced sleep.

a fatigue pattern in the ultralow-frequency ballistocardiograms than in the direct-body ballistocardiograms. With 1 to 3 hours of fatigue, however, all showed the presence of continuous high-frequency oscillations which obscured the ballistic pattern. Four of these fatigue tracings showed deterioration of the ballistic complexes.

Six of these 10 patients were hypnotized. Under hypnosis, it was suggested that they were very uncomfortable and tired. With this suggestion, all 6 tracings showed the same type of continuous high-frequency oscillations; and in 2, the ballistic pattern became completely obscured. While still under hypnosis, the patients were told to relax, and the ballistocardiograms returned to the prefatigue pattern. This technique had the advantage of permitting held respiration even though the patients were asleep.

Four of these 10 patients were given sodium Amytal. When sleep was induced, each tracing returned to its prefatigue state.

Fig. 4 is taken from the tracings of the same 42-year-old male with thyrotoxic heart disease. It shows comparable ultralow-frequency ballistocardiograms with the patient at rest, and with the patient relaxed under hypnosis. Then the posthypnotic suggestion was made that the patient would be tired and uncomfortable, and he was awakened. The ultralow-frequency ballistocardiogram taken during this posthypnotic fatigue shows deterioration of the complexes and interference by high-frequency oscillations. The tracing taken with the patient breathing quietly during the sodium Amytal induced sleep shows complete disappearance of these high-frequency oscillations.

The ultralow-frequency ballistocardiograms of a 44-year-old male with hypertension are shown in Fig. 5. The tracings taken during the control period of rest and those taken with the patient relaxed under hypnosis are similar. The tracings taken with the patient complaining of fatigue, which had been suggested under hypnosis, shows deterioration of the ballistocardiogram and the appearance of small high-frequency oscillations. This patient's blood pressure remained stable throughout the experiment.

Fig. 6 shows tracings taken from the same hypertensive patient. The ballistocardiogram taken after 2 hours and 10 minutes of lying on the ultralow-frequency bed shows deterioration of the ballistic complexes not unlike that produced by having the patient tighten his back muscles voluntarily.

DISCUSSION

It was a purpose of these experiments to produce fatigue or stress in order to change body linkage systems without directly affecting cardiovascular function. The time required to produce fatigue abnormalities in the ballistocardiogram seems excessive in terms of the usual routine recording time necessary to take a ballistic tracing. The long fatigue or stress period, however, has its clinical corollary in anxiety states. That such a relationship is present is evident in the prefatigue tracings of our normal group. Three of these tracings were abnormal even though the patients had no evidence of heart disease. These

3 patients were considered by the psychiatrist to have anxiety states. The fact that their ballistocardiograms became normal with sodium Amytal sleep further supports this concept.

The development of fatigue abnormality in the direct-body ballistocardiogram might be interpreted as evidence of change solely in the external linkage between the body and the table. The presence of definite distortion in the ultralow-frequency ballistocardiogram, however, indicates that internal linkage systems must be involved as well.

In any case, these observations indicate that fatigue or anxiety may produce significant abnormalities of direct-body or ultralow-frequency ballistocardiograms which must be differentiated from abnormalities due to heart disease.

This conclusion suggests an important hypothesis (M.T.): In the presence of a normal heart and great vessels, a relaxed internal body linkage system permits a rhythmic ballistocardiogram. Thus, the extracardiovascular body system is in synchrony with the pulsating heart and, therefore, represents a minimum load on the heart. This phenomenon is analogous to a swing which is periodically given a push. As long as the frequency of the swing is in synchrony with the periodic push, the force necessary to move the swing is minimal. If the frequency of the swing is altered, asynchrony develops. Hence, the force necessary to impart motion to the swing is increased. Under stress, changes take place in the internal body linkages producing an arrhythmia. This arrhythmia represents asynchrony between random mechanical oscillations of the body and the pulsating heart. Therefore, these body movements represent an added load on the heart. It becomes evident, from this hypothesis, that stress over a long period of time may provide a considerable increase in cardiac work load. If this is the case, an abnormal ballistocardiogram becomes significant even though the heart at that particular time is normal.

SUMMARY

Abnormalities were produced in the direct-body and ultralow-frequency ballistocardiograms of patients with and without heart disease, by the induction of fatigue. These abnormalities were obliterated during sleep induced by sodium Amytal and during relaxation under hypnosis.

The changes in these ballistocardiograms are considered to be due to changes in body linkage systems, and not to any abnormality of the heart.

An hypothesis is presented which suggests that the abnormal ballistocardiogram, characterized by a nonrepetitive pattern, reflects asynchrony between the heart and the body. This asynchrony represents an added work load on the heart.

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VISUALIZATION OF THE EXCISED HUMAN HEART BY MEANS OF REFLECTED ULTRASOUND OR ECHOGRAPHY

PRELIMINARY REPORT

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MINNEAPOLIS, MINN.

INTRODUCTION

IT IS the purpose of this preliminary communication to describe some experiments on the excised fresh human heart using the techniques of pulsed ultrasonics known as echography.[1] The principles of echography have been described elsewhere[2,3,4] in connection with the diagnosis of cancer. Briefly, the system consists of a transmitter, a piezoelectric crystal which generates and receives ultrasound, a receiver, and a cathode-ray tube display unit. The echograph operates somewhat like a radar system, except that ultrasound is employed instead of radio waves.

As a preliminary step towards visualizing the cardiovascular system in the living subject, instrumentation originally developed for the examination of "lumps" in the human breast was used.

EXPERIMENTAL PROCEDURE

Immediately following death, the heart was removed from a 56-year-old white man who had been admitted to hospital in shock and expired 35 minutes after admission. The instrument shown in Fig. 1 was applied in such a way that the beam of sound swept over the left coronary artery. The collected results of this procedure are shown in Fig. 2. The left coronary artery was visualized as indicated. The heart was turned over and the base of the heart was scanned as shown in Fig. 3,*B*. The echogram showed the aorta as indicated. The instrument was then applied to the posterior surface of the heart over an area which was seen by the pathologist to be damaged by infarction. The echogram obtained from this procedure is shown in Fig. 3,*A* and the infarct is indicated in the echogram.

Pathologic Report.—The heart was then submitted to routine pathologic dissection and the report on the condition of the heart was as follows:

> Area of softening and hemorrhage in the posterior mid-portion of the left ventricle near the septum. Heart markedly fatty, left ventricle 1 to 1.5 cm. thick. Coronary orifices slightly reduced in size. Dissection of the coronary arteries reveals marked intimal thickening and calcification of the left coronary artery at its most proximal portion. The lumen is pin point in size.
>
> Diagnosis: Coronary sclerosis, coronary thrombosis, myocardial infarction.

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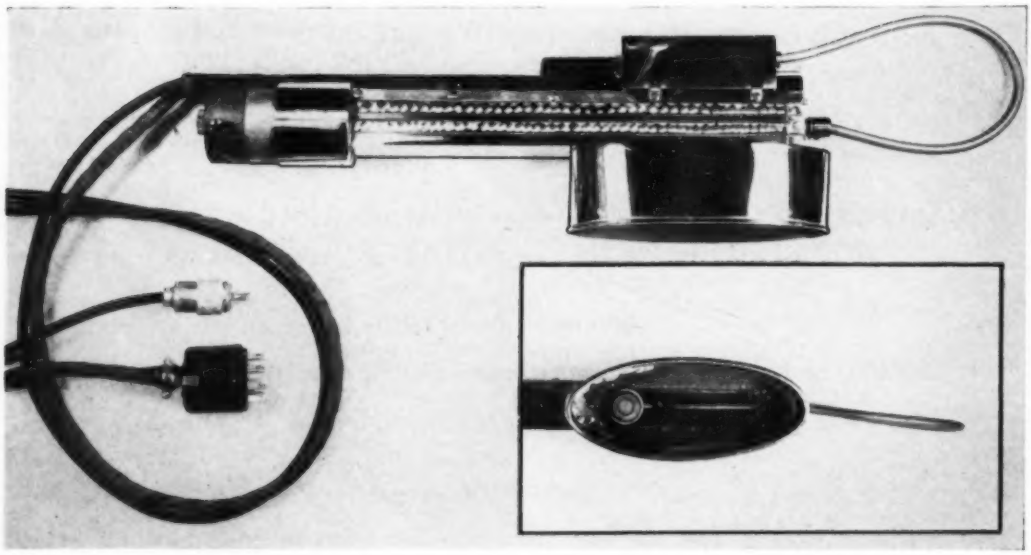

Fig. 1.—A side view of the echoscope used is shown at the top. The inset shows a view into the water chamber with the crystal in the base at the left. The crystal travels back and forth sweeping a distance of 6.5 cm. In use, the water chamber is closed by a rubber membrane permeable to ultrasound

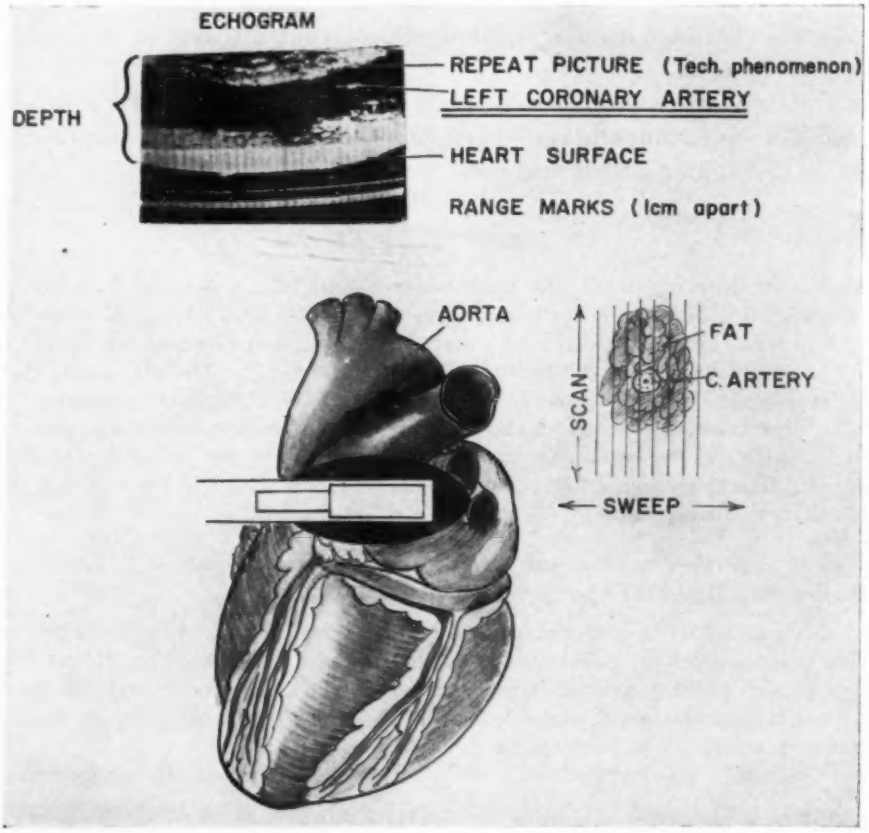

Fig. 2.—Visualization of left coronary artery in excised human heart. The left coronary artery was revealed as a flat group of signals in the echogram as indicated at a depth of approximately 2 cm. from the cardiac surface.

DISCUSSION

The direct visualization of the pathologic condition of the heart in the fresh, warm, human heart was successful from the technical point of view. However, visualizing such conditions in the living, intact subject presents formidable technical problems which must be solved. Two possible approaches have been considered—from the chest wall and from the esophagus. The motion of the living heart can be stopped by electronic timing devices loosely analogous to stroboscopy. Acoustically, limitations are imposed on the system with regard to frequency of operation and range or depth of penetration. It is desirable to use as high a frequency as possible in order to achieve maximum definition. On the other hand, the higher the frequency used the shorter the range. Thus, many compromises must be made in designing the sound heads. Using commercially available flaw detecting equipment which records echoes on a single time base (equivalent to one scan line in Fig. 2), Edler and Hertz[5] have succeeded in obtaining valuable information from the living heart by applying the crystal of the sound head directly to the skin of the chest over intercostal spaces. These workers felt that it might be possible to diagnose auricular thrombosis. They were able to locate echoes from the blood-heart wall boundaries using a frequency of 2.5

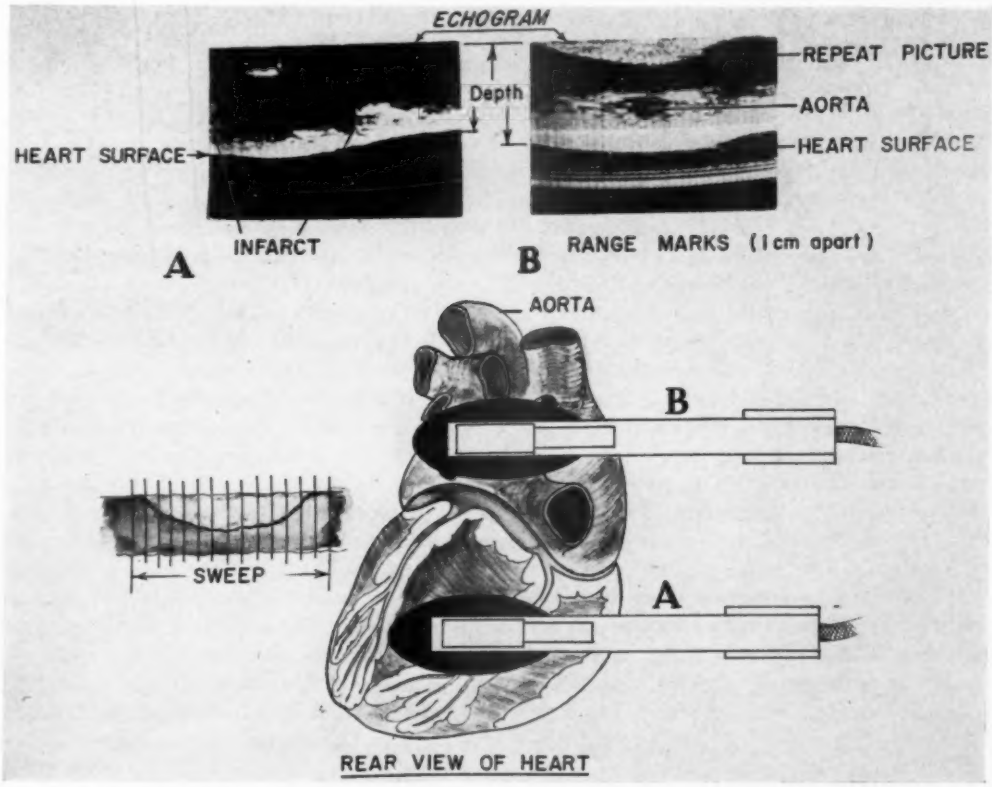

Fig. 3.—Echogram *A*, visualization of infarcted heart muscle; *B*, visualization of base of human heart. The infarcted area was revealed in echogram *A* as a deficiency in the signals in depth as compared with those from contiguous normal cardiac musculature to the right of the indicated infarcted area. The aorta was clearly visualized even with the wide beam width (approximately 9 mm.) used.

megacycles in the living subject and were able to record continuously the movements of the heart wall in normal and diseased states. They also obtained records of the movements of the left atrial wall in mitral stenosis. In a subsequent communication, Hertz and Edler[6] were able to report success in the diagnosis of mitral valve disease by studying records of the heart wall movements. Introduction of the sound head into the esophagus was attempted but abandoned because of difficulty in obtaining acoustic matching between the crystal and the esophageal wall. The use of a water-filled balloon described previously[2] would appear more feasible. Identification of anatomic structures is much easier and certain if the sound beam is swept through the tissues as demonstrated in Figs. 2 and 3.

It would seem that echographic techniques can be applied to the examination of the heart in the living subject if the formidable technical difficulties can be overcome.

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DIURETIC EFFECT OF CHLORPROMAZINE IN PATIENTS WITH CONGESTIVE HEART FAILURE

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ACUTE effect of chlorpromazine* when administered parenterally in normal man and experimental animals usually results in increased urinary flow with little change in the ratio of the clearance of sodium or potassium to the clearance of inulin. This increased water diuresis is not usually associated with a change in renal hemodynamics,[1] although glomerular filtration and effective renal plasma flow may in some cases decrease. The increase in the urine output without increase in electrolyte excretion has found its explanation in a concomitant decrease in urinary excretion of an antidiuretic substance.[2]

The present study was undertaken to determine whether chlorpromazine would also cause diuresis in patients with congestive heart failure who are known to excrete large amounts of antidiuretic substance.[3]

MATERIAL AND METHODS

The subjects studied included a control group of 7 patients without clinical evidence of cardiac or renal disease or hypertension (Group I), 5 patients with congestive heart failure which was due to hypertensive cardiovascular disease in 3 and to aortic insufficiency in 2 (Group II), and 10 patients with chronic cor pulmonale in congestive failure (Group III).

The excretion of water, Na, Cl, and K, were determined in all patients before, during and after continuous i.v. infusion of chlorpromazine. The glomerular filtration rate (GFR) was determined in most of the patients from the creatinine and inulin clearances. Two separate intravenous infusions were set up, one of 5 per cent glucose and the other of 6.0 per cent inulin in 5 per cent glucose, and each was run at 0.5 c.c. per minute. A priming dose of 45 c.c. of the latter solution was given i.v. The bladder was emptied through an indwelling catheter 20 minutes after the start of the infusion, and pressure over the symphysis pubis was applied to insure complete emptying. After collection of urine during 3 successive periods of 15 minutes each, an infusion of 3.5 mg. chlorpromazine in 30 c.c. of 5 per cent glucose replaced the glucose infusion and was run at the same speed. Urine collections were continued at intervals of 15 minutes until a definite diuretic effect was established. The chlorpromazine infusion was then replaced by the 5 per cent glucose infusion and urine was collected for 3 more 15 minute periods. Venous blood was taken for determination of creatinine and inulin, before administration of chlorpromazine, during the diuretic effect, and after chlorpromazine was discontinued. In the cases where no diuresis appeared, blood was taken 120 minutes after starting the chlorpromazine and just before it was discontinued.

Urinary Na and K were determined by means of the Barclay flame photometer. Cl was determined by the method of Schales and Schales,[4] creatinine by the method of Hare,[5] and inulin by a modification of Roe's method.[6]

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*Largactyl-Specia (dimethylaminopropyl-N-chlorpromazine hydrochloride).

Blood pressure was measured by mercury sphygmomanometer every 10 minutes during the experiment, and in 5 cases of cor pulmonale, the ECG was recorded before, during, and after the diuretic effect of chlorpromazine.

TABLE I. EFFECT OF CHLORPROMAZINE (CP)* ON URINARY FLOW (C.C./MIN.)

CASE NUMBER	BEFORE CP (45 MIN.)	DURING CP			AFTER CP (45 MIN.)
		FIRST 45 MIN.	SECOND 45 MIN.	THIRD 45 MIN.	
		Group I: Controls			
1	1.80	1.70	2.48	3.90	1.13
2	1.00	1.16	1.60	4.72	0.90
3	0.84	1.60	1.73	5.22	0.85
4	0.93	1.15	4.50	5.55	0.60
5	1.20	1.00	1.38	4.68	0.80
6	1.30	1.75	2.00	4.95	1.00
7	0.95	1.00	1.80	3.50	0.80
Average	1.15	1.27	2.71	4.56	0.87
S.D.	0.32			0.91	0.15
p†				<0.0001	
		Group II: Congestive Failure Due to Hypertension or Aortic Insufficiency			
1	0.98	0.91	0.67	0.74	0.87
2	0.78	0.67	0.71	0.62	0.38
3	0.60	0.46	0.53	0.37	0.57
4	1.30	0.93	1.11	1.26	0.91
5	0.35	0.32	0.35	0.41	0.35
Average	0.80	0.66	0.67	0.68	0.61
S.D.	0.36			0.129	0.24
p†				>0.05	
		Group III: Congestive Failure Due to Cor Pulmonale			
1	1.03	2.17	5.81	5.06	1.86
2	0.13	0.33	1.67	4.10	1.56
3	0.30	1.51	2.58	1.55	0.78
4	0.53	0.64	1.11	2.23	1.45
5	0.80	0.41	3.52	4.72	1.11
6	0.38	0.49	4.72	2.66	0.30
7	0.87	0.98	3.11	4.92	1.00
8	0.70	0.95	1.13	2.91	1.90
9	0.47	0.94	1.68	2.00	——
10	0.55	1.20	0.82	1.60	0.60
Average	0.58	0.96	2.62	3.175	1.18
S.D.	0.26			1.256	0.53
p†				<0.0001	

*Chlorpromazine administered as a continuous i.v. infusion 3.5 mg./30 c.c. 5 per cent glucose per hour.

†Applies to difference between 45 min. control period and third 45 min. period during chlorpromazine infusion.

Note: Footnotes to Table I apply likewise to Tables II, III, IV, and V.

In analyzing the results, the control urine excreted during the 45 minutes before starting the chlorpromazine infusion was compared with the amount for the third 45 minute period after the start of the chlorpromazine infusion, and with the urinary output for the 45 minutes after discontinuing the infusion. Each of these 45 minute periods consisted of 3 consecutive 15 minute periods of urine collection.

Most of the patients were calm and slept comfortably during the administration of the drug.

TABLE II. EFFECT OF CHLORPROMAZINE ON Na EXCRETION (μEQ./MIN.)

CASE NUMBER	BEFORE CP (45 MIN.)	DURING CP			AFTER CP (45 MIN.)
		FIRST 45 MIN.	SECOND 45 MIN.	THIRD 45 MIN.	
		Group I: Controls			
1	0.166	0.158	0.200	0.250	0.178
2	0.124	0.218	0.178	0.111	0.054
3	0.223	0.254	0.282	0.157	0.200
4	0.171	0.250	0.164	0.127	0.117
5	0.140	0.130	0.163	0.215	0.153
6	0.160	0.185	0.170	0.140	0.142
7	0.190	0.200	0.160	0.135	0.120
Average	0.168	0.200	0.189	0.162	0.138
S.D.	0.032			0.061	0.04
p				0.4	
		Group II: Congestive Failure Due to Hypertension or Aortic Insufficiency			
1	0.146	0.138	0.080	0.104	0.171
2	0.143	0.142	0.143	0.121	0.131
3	0.012	0.015	0.017	0.021	0.018
4	0.227	0.151	0.158	0.158	0.096
5	0.070	0.073	0.072	0.060	0.066
Average	0.120	0.104	0.094	0.093	0.096
S.D.	0.084			0.03	0.05
p				0.05	
		Group III: Congestive Failure Due to Cor Pulmonale			
1	0.088	0.213	0.235	0.180	0.136
2	0.017	0.004	0.019	0.024	0.042
3	0.027	0.126	0.130	0.140	0.066
4	0.058	0.060	0.068	0.058	0.057
5	0.003	0.002	0.017	0.049	——
6	0.008	0.010	0.023	0.039	0.009
7	0.080	0.090	0.095	0.058	0.012
8	0.074	0.067	0.062	0.066	0.057
9	0.019	0.023	0.077	0.093	——
10	0.039	0.040	0.049	0.080	0.040
Average	0.041	0.064	0.078	0.079	0.052
S.D.	0.032			0.0448	0.013
p				<0.01	

RESULTS

A definite and marked diuresis followed the administration of chlorpromazine in the control Group I. The diuresis was usually well developed by 90 minutes after the start of the chlorpromazine infusion, although in a few cases it appeared even earlier. The urinary output during the third 45 minute chlorpromazine period was more than 4 times that of the control period (Table I). The urinary

TABLE III. EFFECT OF CHLORPROMAZINE ON Cl EXCRETION (μEQ./MIN.)

CASE NUMBER	BEFORE CP (45 MIN.)	DURING CP			AFTER CP (45 MIN.)
		FIRST 45 MIN.	SECOND 45 MIN.	THIRD 45 MIN.	
		Group I: Controls			
1	0.200	0.152	0.183	0.129	0.191
2	0.115	0.250	0.218	0.089	0.196
3	0.236	0.225	0.312	0.233	0.190
4	0.378	0.230	0.175	0.131	0.109
5	0.171	0.130	0.183	0.110	0.150
6	0.193	0.300	0.200	0.150	0.160
7	0.230	0.220	0.300	0.227	0.250
Average	0.218	0.215	0.224	0.153	0.178
S.D.	0.084			0.085	0.041
p				<0.05	
		Group II: Congestive Failure Due to Hypertension or Aortic Insufficiency			
1	0.165	0.153	0.101	0.113	0.203
2	0.159	0.155	0.145	0.131	0.138
3	0.009	0.009	0.016	0.021	0.013
4	0.236	0.184	0.160	0.155	0.178
5	0.075	0.077	0.074	0.067	0.073
Average	0.129	0.114	0.099	0.097	0.121
S.D.	0.089			0.036	0.07
p				0.05	
		Group III: Congestive Failure Due to Cor Pulmonale			
1	0.097	0.171	0.246	0.180	0.139
2	0.002	0.004	0.011	0.041	0.030
3	0.027	0.132	0.171	0.142	0.113
4	0.057	0.052	0.065	0.063	0.053
5	0.005	0.002	0.019	0.022	—
6	0.010	0.007	0.017	0.026	0.009
7	0.053	0.060	0.086	0.041	0.013
8	0.089	0.091	0.079	0.091	0.061
9	0.025	0.034	0.108	0.118	—
10	0.057	0.060	0.067	0.079	0.060
Average	0.042	0.061	0.087	0.080	0.060
S.D.	0.032			0.043	0.048
p				<0.01	

flow decreased promptly on cessation of the chlorpromazine and returned to the control rate within about 30 minutes. The water diuresis was not accompanied by an electrolyte diuresis. There was a decrease in Cl and K excretion, but the excretion of Na did not change significantly. The GFR as measured by both creatinine and inulin clearance did not change significantly during the period of diuresis.

TABLE IV. EFFECT OF CHLORPROMAZINE ON K EXCRETION (μEQ./MIN.)

CASE NUMBER	BEFORE CP (45 MIN.)	DURING CP			AFTER CP (45 MIN.)
		FIRST 45 MIN.	SECOND 45 MIN.	THIRD 45 MIN.	
		Group I: Controls			
1	0.164	0.100	0.055	0.088	0.138
2	0.090	0.071	0.052	0.043	0.072
3	0.061	0.080	0.087	0.060	0.072
4	0.052	0.045	0.058	0.040	0.025
5	0.140	0.085	0.048	0.062	0.103
6	0.116	0.092	0.065	0.055	0.120
7	0.052	0.069	0.074	0.052	0.045
Average	0.096	0.077	0.063	0.057	0.082
S.D.	0.045			0.0345	0.038
p				<0.001	
		Group II: Congestive Failure Due to Hypertension or Aortic Insufficiency			
1	0.057	0.045	0.043	0.051	0.040
2	0.062	0.054	0.053	0.051	0.051
3	0.040	0.035	0.034	0.034	0.029
4	0.048	0.035	0.031	0.029	0.032
5	0.032	0.029	0.027	0.035	0.036
Average	0.048	0.040	0.038	0.040	0.038
S.D.	0.014			0.008	0.008
p				>0.05	
		Group III: Congestive Failure Due to Cor Pulmonale			
1	0.033	0.039	0.069	0.048	0.031
2	0.017	0.033	0.032	0.032	0.022
3	0.042	0.084	0.111	0.061	0.041
4	0.029	0.029	0.039	0.037	0.030
5	0.024	0.016	0.031	0.023	——
6	0.010	0.012	0.019	0.024	0.009
7	0.047	0.047	0.070	0.056	0.010
8	0.053	0.047	0.039	0.032	0.019
9	0.058	0.036	0.121	0.103	0.070
10	0.049	0.060	0.054	0.075	0.080
Average	0.036	0.040	0.059	0.049	0.035
S.D.	0.014			0.0172	0.023
p				<0.02	

Among the patients with congestive failure due to hypertension and/or aortic valvular disease (Group II) chlorpromazine had no significant diuretic effect (Table I). There was no change in the excretion of Na, Cl, or K (Tables II, III, IV) nor was there a change in the GFR (Table V).

In the cases of congestive failure due to cor pulmonale (Group III) chlorpromazine produced a marked diuresis (Table I). The urinary flow during the control period of this group was about half that of Group I. However, the maximum diuresis during the third 45 minute period of chlorpromazine administration rose to over 7½ times that of their own control period, although the absolute rate still did not reach that achieved by Group I during chlorpromazine administration. The water diuresis in the patients with cor pulmonale also decreased rapidly after cessation of the chlorpromazine infusion. In contrast with the normal group

TABLE V. EFFECT OF CHLORPROMAZINE ON GLOMERULAR FILTRATION RATE (C.C./MIN.)

CASE NUMBER	CREATININE CLEARANCE			INULIN CLEARANCE		
	BEFORE CP	DURING CP THIRD 45 MIN.	AFTER CP	BEFORE CP	DURING CP THIRD 45 MIN.	AFTER CP
			Group I: Controls			
1	165.00	187.00	175.00	125.00	159.00	143.50
2	130.00	150.50	145.00	102.00	110.00	108.00
3	125.00	120.50	130.00	102.00	98.00	110.00
4	145.00	140.00	150.00			
Average	141.25	149.42	150.00	109.70	122.30	120.50
S.D.	17.97	15.03	16.00	13.26	19.42	16.20
p		0.3			0.3	
			Group II: Congestive Failure Due to Hypertension or Aortic Insufficiency			
1	83.5	90	100.0			
2	35.0	45.0	33.0			
3	34.8	35.4	34.2			
Average	51.1	56.8	55.7			
			Group III: Congestive Failure Due to Cor Pulmonale			
1	35.00	90.00	30.00	30.00	69.00	28
2	30.00	62.00	32.50	28.00	55.00	30
3	39.00	163.00	48.00	34.00	130.00	40
4	41.00	149.00	50.00	35.00	92.00	38
5	47.50	134.00	45.00	45.00	96.50	40
6	23.20	75.80	37.60			
7	29.00	115.00	56.00			
Average	34.96	112.70	42.70	34.40	88.50	35.2
S.D.	8.24	32.76	8.90	6.58	26.134	5.13
p		<0.0001			<0.001	

the water diuresis in patients with congestive cor pulmonale was accompanied by an electrolyte diuresis (Tables II, III, IV) although this was not proportional to the water diuresis (Table I). The Na excretion rose to almost twice that of the control period. The Cl also rose to the same extent, while the K excretion did not increase significantly. The electrolyte diuresis decreased to control period values promptly following cessation of the chlorpromazine infusion. The average GFR in the control period of Group III, as determined by either the inulin or the creatinine method, was less than one fourth that of the control group. During the diuresis induced by chlorpromazine, the GFR of these patients more than doubled (Table V). After cessation of the chlorpromazine infusion the GFR decreased rapidly.

The maximum decrease in blood pressure during the infusion in all groups was in the range of 15 to 20 mm. Hg systolic and 5 to 10 mm. Hg diastolic.

DISCUSSION

The results of the present study demonstrate that chlorpromazine is effective as a diuretic not only in normal individuals, but also in patients with cor pulmonale in congestive heart failure. The water diuresis produced in normal individuals under the present experimental conditions was not accompanied by an electrolyte diuresis. Similar results were found by Moyer[1] and Parrish.[2] However, in contrast to their results there was no decrease in GFR.

The mechanism of this water diuresis has been related to the fact that the amount of antidiuretic substance in the urine decreased as the urinary flow increased.[2]

Unlike the course in normal individuals, the diuresis produced by chlorpromazine in patients with congestive failure due to cor pulmonale was accompanied by an increase in the excretion of Na and Cl. This difference may be explained by the fact that in the patients with congestive failure due to cor pulmonale chlorpromazine increases the GFR to about 3 times that of the control period, while in the normal subject the GFR is unchanged. Thus we can assume that in the patients with congestive heart failure due to cor pulmonale in which increased amounts of antidiuretic substances were found in the urine[3] the drug causes diuresis by a double mechanism: (1) by reducing the secretion of an antidiuretic substance, and (2) by increasing the GFR. However, the possibility of increased water excretion per se causing a secondary increase in electrolyte excretion should be considered.

Potassium excretion did not change during the period of diuresis. This is in line with the fact that potassium excretion in the urine is less dependent on the relative magnitude of the GFR and is more related to tubular function.

The fact that in the patients with congestive heart failure due to cor pulmonale the GFR could be raised indicates that the reduction in GFR in this condition may be reversible. Thus, chlorpromazine which is known to have a powerful vasodilating effect in other parts of the body[7] also appears to be able to abolish functional constriction in the renal vessels. This suggests that the mechanism of heart failure and water retention in cor pulmonale is different from that in congestive failure due to other types of heart disease.

With the dose of chlorpromazine used in this set of experiments, the blood pressure did not change significantly. In preliminary experiments, slightly larger doses of chlorpromazine caused a decrease in blood pressure, and the urinary flow consequently decreased almost to zero. When the rate of administration of chlorpromazine was diminished and the blood pressure rose again to normal, urinary flow increased. It should be clear that the results described above were obtained only with doses of chlorpromazine not large enough to reduce the blood pressure significantly.

The 5 cases of congestive heart failure due to hypertension or aortic valvular disease did not respond with a water diuresis to the dose of chlorpromazine used. The GFR in these cases was slightly higher than in those with cor pulmonale. However, the reason they did not also respond to chlorpromazine with a diuresis is not apparent.

SUMMARY

1. The effect of a continuous intravenous infusion of chlorpromazine on the urinary flow, on the excretion of Na, K, Cl, and on the GFR was studied in a group of patients with congestive failure due to cor pulmonale, in a group with cardiac fallure due to hypertension or aortic insufficiency, and in a group without evidence of cardiovascular or renal disease.

2. In 7 patients without cardiovascular or renal disease there was a marked water diuresis without increase in electrolyte excretion. The GFR did not change.

3. In 5 patients with congestive heart failure due to hypertension or aortic insufficiency, chlorpromazine did not produce a diuresis nor was there an increase in electrolyte excretion or any change in the GFR.

4. In 10 patients with congestive heart failure due to cor pulmonale, chlorpromazine caused a marked water diuresis, but there was also a definite increase in Na and Cl excretion. The GFR rose in most of these cases.

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HIATUS HERNIA AND ELECTROCARDIOGRAPHIC CHANGES

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STIMULATION of the vagus nerve or of hollow abdominal viscera has caused diminished coronary blood flow in animal experiments.[1] Vagal coronary reflexes or, alternatively, a diminution in cardiac output and blood pressure have been held responsible.[2] It is possible that similar effects may occur in human physiology. With regard to hiatus hernia, the opinion has been expressed, "Although we do not believe that hiatus hernia produces any disturbance in the coronary circulation in the presence of normal coronary arteries, it is possible that it may act as a trigger mechanism precipitating angina pectoris when the coronary arteries are sclerotic."[3] In line with this opinion, Segall and associates[4] found striking changes in the T waves, on direct carotid sinus stimulation, only in patients with evidence of impairment of the coronary circulation.

Nevertheless, isolated reports have appeared in the literature suggesting that hiatus hernia may cause significant electrocardiographic changes. Cossio and Fustinoni[5] described 5 cases with "the appearance of a coronary T wave in the E.C.G. . . . due to mechanic or inflammatory action of the hernia on the pericardial surface of the heart." Jansoni and Bertiglia[6] described temporary T-wave changes in Lead I which they believed were due to vagal coronary reflexes from a hiatus hernia. Parsonnet, Klosk and Bernstein[7] described a 51-year-old patient with a demonstrable hiatus hernia and evidence of previous myocardial infarction.

"The swallowing of food was almost certain to bring on an attack of substernal pain which would be relieved by nitroglycerin. During these attacks there was electrocardiographic evidence of acute coronary insufficiency. It is noteworthy that these attacks could not be induced by effort." The published report shows horizontal or sagging S-T segment depression in Leads I and II after "half a slice of toast and half a cup of milk." The changes revert to normal after nitroglycerin.

The following study was conducted in order to determine whether fleeting ECG changes occur with simultaneous visualization of hiatus hernia.

MATERIAL

Fifteen patients with hiatus hernia were studied, as they became available to the x-ray department. Of these patients, 3 were aged 30 to 40; 5 were aged 40 to 50; 5 were aged 50 to 60; and 2 were over 60 years old. Routine ECG showed that 1 patient had evidence of previous myocardial infarction, 1 had left bundle branch block, and 1 had T-wave abnormalities only. Six patients were male and 9 were female.

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X-Ray Technique.—The technique used was that previously described.[8] The patient lies on the x-ray table in the left oblique position in order to separate the densities of the heart and the hernia. A mouthful of barium is swallowed under fluoroscopic control. As the esophagus fills with barium, the patient is instructed to take a deep breath and hold. (Deep inspiration increases the intra-abdominal pressure and decreases the intrathroacic pressure. It is thought that an esophagus "full" of barium exerts a siphon or suction effect on the hernia under the above conditions.)

ECG Technique.—Leads I, aV_F, V_6, and V_8 were recorded simultaneously in a 4-channel Sanborn electrocardiograph. Records were made in the standard supine position, in the oblique position, and in the oblique position with the breath held in deep inspiration. Finally, an ECG was recorded simultaneously with the barium swallow and deep inspiration, in an attempt to visualize the hernia under fluoroscopic control.

RESULTS

Vagal Effects.—At the time of simultaneous ECG study, the hernia was demonstrated in 11 of 15 patients previously known to have hiatus hernia. No vagal effects were demonstrated in any of these 15 cases as judged by observation of the rate and rhythm and measurement of the P waves and the P-R intervals.

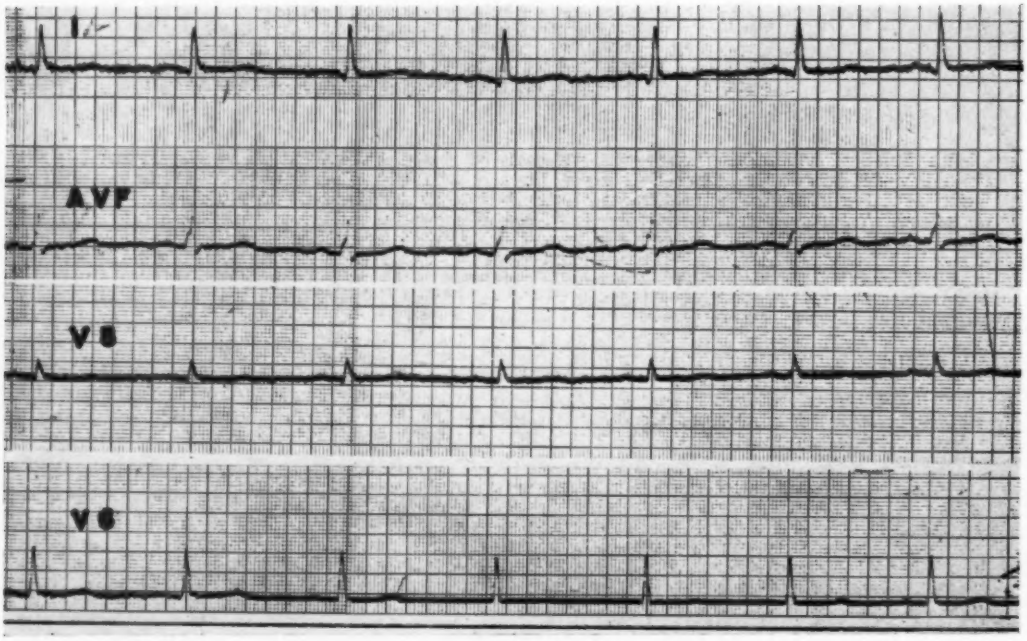

Fig. 1.

QRS and T.—Deep inspiration produced obvious changes in QRS and T in these patients as well as in patients without hiatus hernia. Accordingly, attention was directed to comparison of records in deep inspiration in the oblique position before and during the attempted visualization of the hernia. The records were read without any prior knowledge of the x-ray results.

There were no QRS and T changes that could be attributed to the hiatus hernia. Now, look at the ECG shown in Fig. 1. For convenience of mounting, Leads V_6 and V_8 were cut and remounted. The record was taken at normal

standardization but at twice normal speed (50 mm. per second). Lead V_6 shows a cyclic fading and reappearance of the T wave accompanied by a similar change in the P wave. A simultaneous but less obvious change occurs in QRS. The sinus rhythm remains unchanged (see Lead aV_F).

Throughout, the R-R interval diminishes slightly but progressively. The P-R interval remains unchanged. The x-ray record showed that the hiatus hernia was not visualized on fluoroscopy or in the spot film at the time the ECG was made. In one of the other cases studied, similar T-wave changes were seen, but without a complete cycle of fall and rise; in that case the hernia was clearly demonstrated.

COMMENT

In a recent study[9] it was concluded that "electrocardiographic changes occur as a result of mechanical distention of the stomach or small intestine." Because "the changes were not associated with significant alteration of the QRS axis, nor could they be reproduced by placing the patient in the Trendelenburg position," the author concluded that "the possibility remains that a reflex mechanism is involved." (It must be stated that the publication referred to shows T-wave changes in Lead III which is particularly sensitive to heart movement. Note that the authors claim that the T-wave change is not associated with "significant" QRS change.)

Einthoven, Fahr and de Waart[10] showed that in respiration changes in P and T may not always correlate quantitatively with changes in QRS. In describing the effect of respiration on the mean spatial T vector, Grant[11] commented, "Furthermore in some instances this alteration appeared to be gradual, its completion requiring several complexes after full inspiration had been reached." A report by Frank and Kay,[12] using an artificial dipole on torso models, has emphasized that "the dipole position has a very pronounced effect on the wave shape inasmuch as it results in extreme effects in certain cases such as inverting the Q wave, reducing greatly the R wave or deepening the S wave." In this last report it is seen that change in dipole position alone has reproduced changes classically attributed to rotation of the heart axis. It is obvious that if the equivalent QRS dipole and the equivalent T dipole are located differently, complex results may occur. We believe that reported effects on the T waves of the electrocardiogram due to reflexes originating in the gall bladder, stomach, or hiatus hernia should be accepted with caution.

SUMMARY

Fifteen cases of hiatus hernia were studied by a technique suitable to demonstrate fleeting ECG changes at the time of visualization of the hernia. No changes were observed that could be ascribed to reflex or mechanical effects arising in hernia.

Many of the patients studied were in the age group in which significant coronary arteriosclerosis is common. Three of the patients studied had abnormal routine electrocardiograms.

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RESPIRATORY CHANGES OF THE SPATIAL VECTORCARDIOGRAM RECORDED WITH DIFFERENT LEAD SYSTEMS

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INTRODUCTION

RESPIRATORY effects on the electrocardiogram were observed in the very early phases of electrocardiography,[1-4] and were studied systematically by Einthoven in 1913.[5] The early studies and most of those that followed have been concerned with respiratory variations determined in the frontal plane with the aid of the three standard leads.[5-8,11-16] There is agreement that the downward rotation of the QRS and T axes in inspiration increases with increasing initial (mid-respiratory) left axis deviation.[6-10] Oscillographic loop projections on two planes (frontal and sagittal) in different respiratory positions were obtained by Schellong,[10] Vastesaeger,[9] and Burch,[17] and on one plane by Hollmann and Guckes.[11] In all of these studies, changes of the loop contour were noted together with changes in axis orientation. Most of the investigators[5,10-13] explained the respiratory electrocardiographic changes on the basis of positional changes of the heart, but some authors[12,14,15] held that nervous and hemodynamic factors, such as diastolic volume changes, are involved. No adequate statistical evaluation of respiratory electrocardiographic changes has been made, however, in previous studies.

Spatial vector analysis, as contrasted to analysis of projected planar vectors, permits a quite accurate characterization of directional changes and a more precise differentiation between positional and functional changes. Actual spatial vectors must be determined, and not merely their projections in one or the other plane, for these are nearly as sensitive to positional variability as are single leads. No such studies have yet been reported.

The advantages of spatial vectorcardiography are fully realized, however, only with a lead system projecting the horizontal, vertical, and sagittal components with a minimum of distortion. Since the lead systems currently most popular (conventional leads, Duchosal, Wilson-Burch, Grishman, etc.) are demonstrably mutually inconsistent and in all probability share a large element of distortion,[19] the results obtained with different systems are not directly compara-

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ble. As in any type of vectorcardiographic work, it would be desirable to use leads in such a way that generalization of conclusions could be made that are not dependent on the lead system per se.

The present study is comprised of three parts. The bulk of the experimental material was obtained with mean spatial QRS and T vectors, constructed from conventional leads with a mechanical analyzer,[18] and is presented in the first part. The justification for using the conventional lead system is its universal acceptance in clinical electrocardiography.

In the second part, the results are compared with the SVEC III lead system. This system, consisting of 3 electrically orthogonal leads (X, Y, Z), shows the least distortion of all lead systems compared. It is developed by combining several lead positions (4 for lead X, 8 for lead Z), thereby cancelling the distortions in the separate lead components.[19] SVEC III, therefore, probably comes closest to a practically realizable ideal lead system. In addition, exploratory comparisons were also made with 6 other lead systems.

In the third part, an attempt is made to explore the mechanisms of respiratory changes. Studies of quantitatively fractionated respiration and comparison of regular beats and ventricular extrasystoles are included.

METHOD

The mean spatial vectors, both for the conventional and the SVEC III lead system, were determined from time-based electrocardiograms using a mechanical vector analyzer.[18] The 14 electrode positions for the SVEC III system are described in an earlier communication.[19] Because of the numerous electrodes required, a vest was constructed which permits all necessary electrodes

Fig. 1.—The vest with adjustable electrodes clipped to elastic bands with spring coil fasteners.

to be attached in a single simple procedure. It consists of an array of elastic belts,[25] as shown in Fig. 1. The individual electrode positions are adjustable by moving the electrodes along the elastic bands and by adjusting whole bands according to body build. The whole procedure, i.e., putting on the vest, applying electrode paste, taking 3 standard leads, the 3 SVEC leads, and Leads V_1-V_6 is done within 8 to 10 minutes. A 4-channel Sanborn machine was used in conjunction with a special switch network which permits instantaneous selection of any 4 groups of 4-lead sets: in this case, Leads I-III, X-Y-Z, V_{1-3}, V_{4-6}, each plus one common reference lead, Y, were used.

In a smaller number of subjects, oscilloscopic spatial loops were recorded and maximum QRS and T vectors determined by rotation of projection, as described in an earlier communication.[20] In addition, the loops were photographed in their maximum projection and in projection on frontal, horizontal, and sagittal planes. The following lead systems were compared: conventional leads, SVEC II, SVEC III, Briller, Duchosal, Frank, Grishman, Wilson-Burch.

In all subjects, the records were taken in mid-respiration (MR), in full inspiration (IN), and in full expiration (EX). A more quantitative study was made with 5 subjects using fractionated inspiration of 1,000, 2,000, 3,000 c.c., covering the whole range of vital capacity, as measured by a spirometer.

The values are given in terms of elevation: V° (90° left; 0° down); azimuth H° (0° left, 90° front, −90° back); magnitude (Mag., standardized mm. = 0.1 mv.); and the angle between the spatial QRS and T vectors (dA°).

Subjects.—The main experimental group consisted of 38 healthy men from 19 to 63 years old, with a mean age of 42.8 years. The subjects were selected so as to cover the normal range of distribution QRS-V°, in mid-respiration (MR), from 8° to 102°, and QRS-H° from −64° to 35°. The means and standard deviations of the various items were nearly identical with those of a larger group of 178 healthy men previously published.[22] The group of 38 men is, therefore, fairly representative of normal means and distribution as obtained in the larger group. Comparison of the conventional lead system and SVEC III was made in another group of 22 healthy men.

RESULTS

Part 1: Respiratory Changes of Mean QRS and T Vectors, Conventional Lead System.—

Table I shows direction and magnitudes of mean QRS and T vectors in mid-respiration (MR), maximal inspiration (IN) and maximal expiration (EX) the mean differences between MR and IN, and MR and EX positions. The statistical significance of these differences, as evaluated by means of the t-test, is also tabulated.

Since the volume change associated with full inspiration is much larger than that produced in expiration, it is not surprising that the changes in expiration are smaller than those in inspiration. The trends of the changes of H° and of V° with inspiration are statistically significant for both QRS and T vectors in spite of considerable individual variability. In expiration the changes of QRS and T-H° are in general opposite, but smaller. Although the mean changes of QRS-Mag. and T-Mag. are statistically not significant, the large standard deviations show that in some subjects the changes of the vector magnitude are quite large (the extreme changes were −7.3 mm. for QRS and +5.0 mm. for T). It is of interest that dA° increases significantly in inspiration. This cannot be explained simply by a positional factor for, in an ideal lead system, dA° would presumably be independent of position.

The most surprising result is the statistically highly significant rotation of QRS-H° and T-H° in opposite direction, shown in Fig. 2, QRS-H° moving backward and T-H° forward in inspiration. Clearly, this cannot be explained on the basis of positional change.

There is also an inconsistency in the elevational mean shifts of QRS and T (Fig. 3), but in this case the gross rotations are not opposite in direction. The shift is larger for QRS than for T; the difference of 12.0° is statistically significant at the 0.1 per cent level.

Larger changes of the Einthoven QRS axis than of the T axis in inspiration were noted by previous investigators,[5,6,12,24] but were explained on a positional basis. Having observed the discrepancies in the directional changes of the QRS- and T-vector projections, we must expect accompanying changes in dA°.

Fig. 2 shows the average respiratory changes of QRS-H° and T-H° in 38 men. The individual difference in the direction of QRS-H° and T-H° reached an extreme of 48°. The values refer to mean vectors determined from conventional leads. Fig. 4 shows an example of the opposite movement of the QRS and T null point in the precordial leads.

There was a highly significant negative correlation between V° in MR position and the changes in IN position both for QRS and T. The changes of QRS-V° in inspiration were also correlated to those of T-V° in MR. The correlation coefficients and regression equations are shown in Table II. Fig. 5 shows, in a scatter diagram, the relationship between QRS-V° in MR position and change in IN position. The dashed lines demarcate the predicted 95 percentile limits which were used for the evaluation of respiratory changes in patients. The greater changes accompanying higher elevational angles support former observations of respiratory changes of the Einthoven axes.[6-10]

TABLE I. MEAN VALUES (M) AND STANDARD DEVIATIONS (S.D.) OF THE MEAN SPATIAL QRS AND T VECTORS OF 38 HEALTHY MEN IN MID-RESPIRATION (MR), MAXIMAL INSPIRATION (IN) AND MAXIMAL EXPIRATION (EX). CHANGES (MEAN DIFFERENCES, MΔ) FROM MR TO IN (ΔIN-MR) AND FROM MR TO EX (ΔIN-EX)

	QRS			T			dA°
	H°	V°	MAG. (mm.)	H°	V°	MAG. (mm.)	
MR							
M	−20.3	50.2	10.21	46.4	63.9	3.94	56.0
S.D.	24.2	28.9	3.73	13.6	19.6	1.47	20.6
IN							
M	−28.8	33.7	9.51	55.9	59.4	3.43	61.3
S.D.	24.9	19.6	3.82	14.4	18.2	1.84	21.9
EX							
M	−16.8	56.5	10.33	44.1	67.1	4.07	56.9
S.D.	22.1	27.6	4.14	12.7	18.9	1.67	19.5
ΔIN-MR							
MΔ	− 8.5	−16.5	− 0.70	9.5	− 4.5	−0.51	5.24
S.D. of Δ	7.5	14.6	2.47	8.1	13.5	1.58	13.9
t_{n-1}	6.925***	6.949***	1.748	7.280***	2.048*	1.977	2.330*
ΔEX-MR							
MΔ	3.5	6.3	0.12	− 2.3	3.2	0.13	0.9
S.D. of Δ	9.4	15.6	1.75	6.4	11.7	2.18	11.6
t_{n-1}	2.321*	2.468*	0.418	2.189*	1.693	0.363	0.446

H°—azimuth angle; V°—elevation angle; and dA°—spatial angle between mean QRS and T vectors.
Statistical significance evaluated by the t-test: * $P_t < 0.05$
** < 0.01
*** < 0.001

A further analysis of respiratory effects on vector directions was made by comparing positional subgroups. The basis for their selection is shown in Table III. Only the changes from MR to IN position were analyzed.

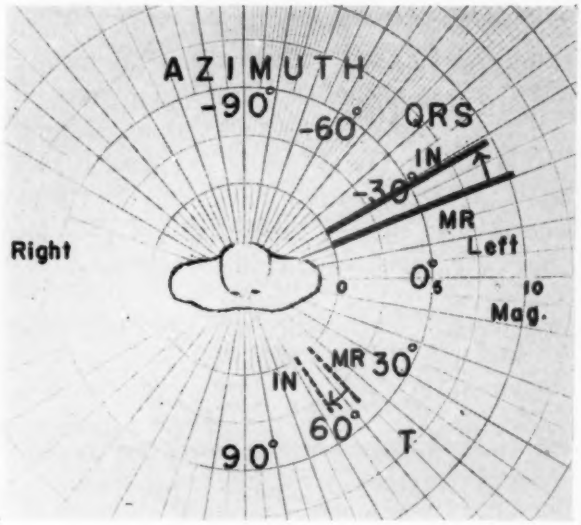


Fig. 2.—The average changes (arrow) of the azimuth QRS-H° and T-H° in 38 men from mid-respiration (MR) to inspiration (IN). Length of the vectors indicates spatial magnitudes of mean QRS and T vectors and not of their projections on the horizontal plane. QRS-H° and T-H° rotate in opposite directions.

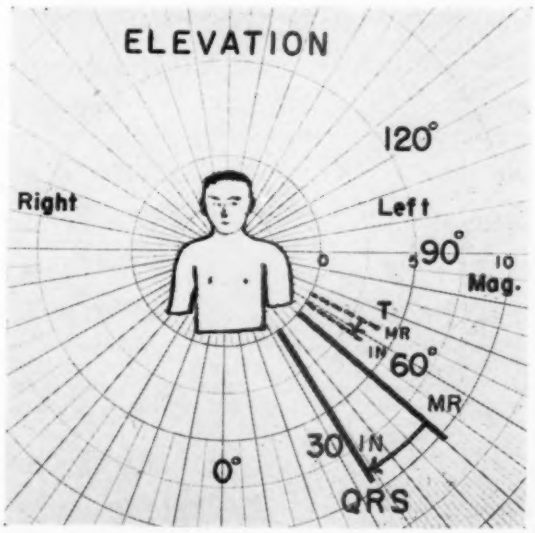


Fig. 3.—The average changes (arrow) of the elevation QRS-V° and T-V° in 38 men from MR to IN. Length of the vectors indicates spatial magnitudes of mean QRS and T vectors and not of their projections on the frontal plane. The rotation of QRS vector exceeds that of T vector.

Table IV compares 11 men with horizontal and 11 men with vertical QRS vector. The average changes of QRS-V° in the horizontal group (−30.7°) are much larger than those in the vertical group (−5.1°), as expected from the correlation in Table II. T-V° does not change in the vertical group, but moves significantly downward in the horizontal group. The orientation of QRS-V° is also related to the rotation of QRS-H°, which is significantly greater in the vertical group (−12.3 vs. −5.7). In contrast to the orientation of V° in MR position, the orientation of H° is not related to changes in inspiration (Table V).

In the horizontal T-V° group the inspiratory changes of V° were significantly larger for QRS-V° (−29.1°) and T-V° (−13.3°) than in the vertical T-V° group (QRS-V° −6.9°; T-V° +5.2°). These results are similar to the comparisons of the vertical and horizontal QRS groups. Similarly, the rotation of QRS-H° was larger (−12.3°) in the vertical than in the horizontal T-V° group (−5.5°). This difference did not, however, reach statistical significance.

TABLE II. CORRELATION AND REGRESSION BETWEEN VARIOUS VECTORIAL ITEMS

	COEFFICIENT OF CORRELATION	INTERCEPT ON ORDINATE	SLOPE	STANDARD ERROR	2 S.E.
$QRS\text{-}V°_{MR}$ *vs.* $\Delta QRS\text{-}V°_{IN\text{-}MR}$	−0.78**	3.4	−0.40	9.1	18.2
$T\text{-}V°_{MR}$ *vs.* $\Delta T\text{-}V°_{IN\text{-}MR}$	−0.45**	15.3	−0.31	12.1	24.2
$\Delta T\text{-}V°_{IN\text{-}MR}$ *vs.* $\Delta QRS\text{-}V°_{IN\text{-}MR}$	0.47**	−14.2	0.51	13.1	26.2

**For statistical significance see Table I.

TABLE III. CRITERIA FOR SELECTION OF EXTREME CASES AND NUMBER IN EACH POSITIONAL GROUP

QRS	CRITERION	NUMBER
Vertical QRS vector group	$QRS\text{-}V°_{MR} \leqq 30°$	11
Horizontal QRS vector group	$QRS\text{-}V°_{MR} \geqq 70°$	11
Clockwise rotation QRS vector group	$QRS\text{-}H°_{MR} \leqq -40°$	6
Counterclockwise rotation QRS vector group	$QRS\text{-}H°_{MR} \geqq +5°$	8
T		
Vertical T vector group	$T\text{-}V°_{MR} \leqq 48°$	7
Horizontal T vector group	$T\text{-}V°_{MR} \geqq 80°$	10
Clockwise rotation T vector group	$T\text{-}H°_{MR} \leqq 33°$	8
Counterclockwise rotation T vector group	$T\text{-}H°_{MR} \geqq 60°$	9

Comparison of additional subgroups selected for clockwise and counterclockwise orientation of T-H° in MR position did not reveal significant differences for the vectorial changes in inspiration.

For analysis of age effects, 14 young men between 19 and 29 years were compared with 14 older men between 57 and 63 years. It has been shown in previous communications that age and electrical heart axes are not independent.[23] The mean respiratory changes of QRS- and T-Mag. were not significant, however, in the total or in any of the positional groups, and they were also not significant in either age groups.

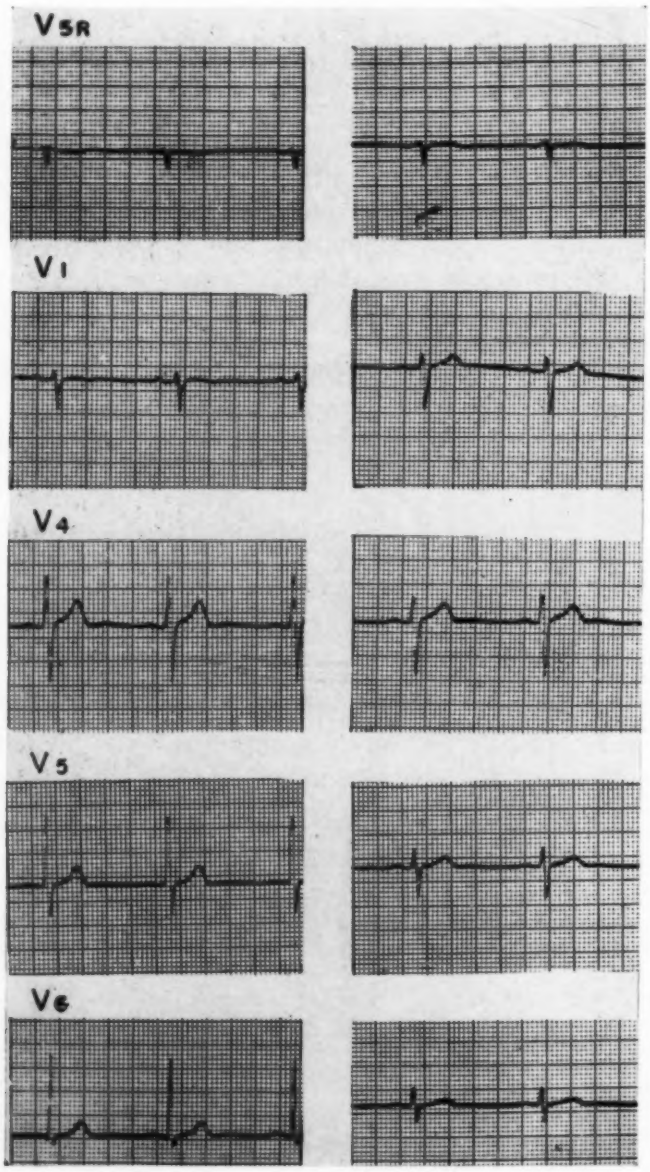
The effect of age on the direction of V° in MR position was corrected with the aid of the regression equation of Table II. QRS-V° in MR for the young group was 28.9°, and changed in IN position to 19.4°. The change of −9.5° exceeds slightly the predicted value of −8.0° (for 28.9° in MR). In the older group, QRS-V° in MR was 63.6° and changed to 46.4° in IN position. The difference −17.2° is somewhat smaller than the predicted value of −21.8°. These slight differences were not statistically significant, and this is also true for the other vectorial items. We must conclude that age seems not to influence respiratory changes of spatial QRS and T vectors.

TABLE IV. COMPARISON BETWEEN VERTICAL QRS VECTOR AND HORIZONTAL QRS VECTOR GROUPS†

	QRS			T			dA°
	H°	V°	MAG.	H°	V°	MAG.	
Vertical QRS Vector Group							
MR M	−27.8	19.9	10.3	51.1	51.7	4.08	53.2
S.D.	22.3	5.7	3.84	13.2	18.5	1.59	18.7
IN M	−40.1	14.8	10.9	58.7	53.4	3.63	57.6
S.D.	19.1	4.0	2.90	15.8	16.1	2.10	18.1
MΔ	−12.3	− 5.1	0.6	7.7	1.7	−0.45	4.4
S.D. of Δ	9.3	6.6	—	6.9	10.0	—	7.6
t_{n-1}	4.353**	2.548*	—	3.686**	0.545	—	1.942
Horizontal QRS Vector Group							
MR M	−21.5	86.3	8.73	41.9	79.4	2.93	64.4
S.D.	23.3	10.5	4.27	15.0	16.6	0.72	23.5
IN M	−27.2	55.6	6.88	51.1	68.4	2.67	69.9
S.D.	24.6	14.8	2.27	17.3	20.7	1.84	33.6
MΔ	− 5.7	−30.7	− 1.85	9.2	−11.0	−1.09	5.5
S.D. of Δ	4.9	10.2	—	7.1	12.1	—	18.4
t_{n-1}	3.844**	9.999***	—	4.317**	3.021*	—	0.998
$t_{n1+n2-2}$	2.070	6.944	—	0.542	2.691	—	0.183
P_t	0.054	0.0001	—	non sig.	0.015	—	non sig.

†Code in Table III.
Statistical significance evaluated by the t-test: *P_t < 0.05
** < 0.01
*** < 0.001

Part 2: Comparison of Respiratory Changes in Different Lead Systems.—In 22 men, the vectorial changes from MR to IN respiratory position were recorded with the conventional and with the SVEC III lead system (Table VI). Both lead systems were recorded on the same occasion, separated by a time interval of less than 1 minute. This group was not included in the group of 38 men studied with the conventional lead system alone, yet the respiratory changes were nearly identical, as shown by comparison of Tables VI and I.



A. *B.*

Fig. 4.—*A*, MR; *B*, IN. The null point of QRS complex located in V_4 in MR shifts to V_6 in IN, while that of T wave moves from V_1 to V_{5R}.

The changes in all items are in the same direction for both systems, but are not identical in extent. The differences are statistically not significant, however, except for the greater increase of dA° with the SVEC III system. The small decrease of QRS-Mag. of −0.49 mm. with the conventional lead system is not significantly different from zero (i.e., no change), while the decrease of −1.60 mm. with the SVEC III system is very significantly different from zero. The difference in QRS-Mag. between the two systems, however, is not statistically significant. The lack of significance for the difference is probably due to the small magnitude of changes, which approach the error of measurement in many cases.

A significant correlation between the respiratory changes in the conventional and SVEC III lead system was found for QRS-H° (correlation coefficient 0.86), QRS-V° (0.52), QRS-Mag. (0.51), and T-H° (0.45). T-V° (0.32) did not quite reach the 5 per cent level of significance. The correlation is closer for QRS than for T, but still too low to predict the changes in one lead system from those in the other lead system (except for QRS-H°).

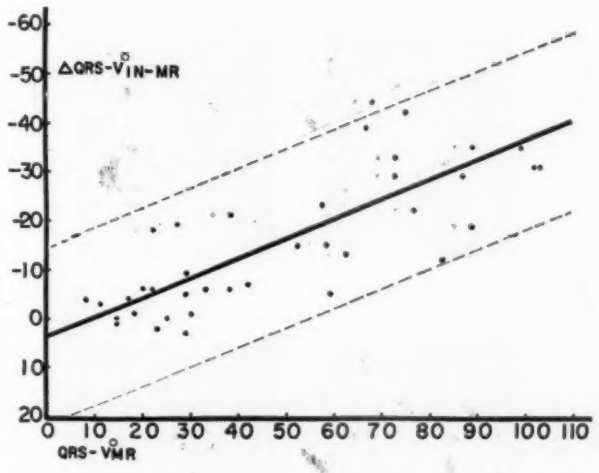


Fig. 5.—Negative correlation between QRS-V° in MR (abscissa) and ΔQRS-V° from MR to IN (ordinate). The thick line indicates regression line and the dashed lines demarcate the predicted 95 percentile limits.

In each of 4 subjects, spatial QRS and T loops were obtained with 7 different lead systems, in addition to conventional and time-based SVEC leads. Fig. 6 shows stereoscopic loop projections on the frontal, horizontal, and sagittal planes taken with the SVEC III lead system. Not only the orientation, but also the configuration, of the loop changes drastically from MR to IN position.

Four out of the 7 different lead systems (SVEC III, Duchosal, Grishman, Wilson-Burch) are compared in Fig. 7, each in a projection displaying a maximal extension of the QRS loop. With this procedure, directional differences are compensated by electronic rotation. The directional angles are read on the azimuth and elevation scales and are inserted in Fig. 7. Even with this procedure, the loop configuration is different for MR and IN position; the change of the QRS

loop contour in any plane (Fig. 6) is, therefore, not due alone to a different angle of projection. Thus, loops of all 4 lead systems have different initial orientation and shape and show different changes of QRS-loop contour with respiration.

We found that the changes in maximal inspiration are not immediately reversible; they persist for a short time (several seconds) after resumption of normal respiration.

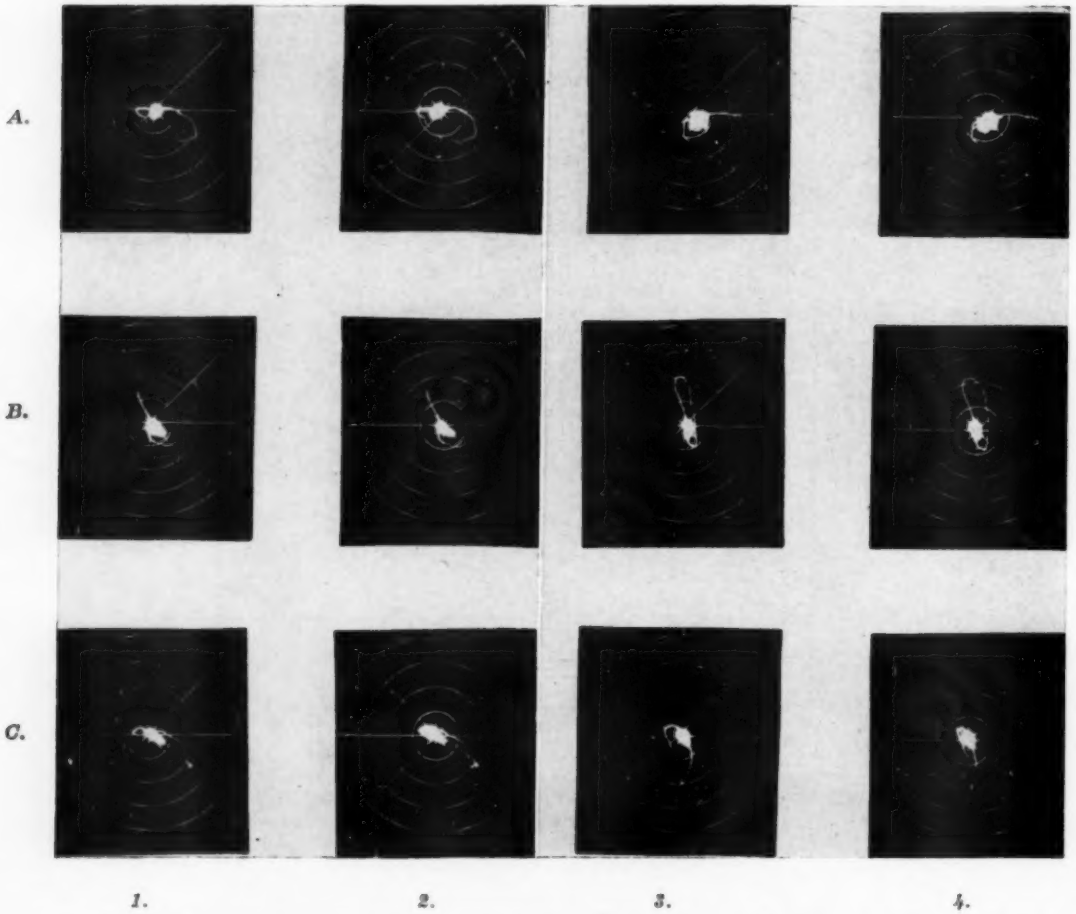


Fig. 6.—Stereoscopic presentation of SVEC III records of one subject, projected on the sagittal (*A*), horizontal (*B*), and frontal (*C*) planes, shows changes in configuration and orientation of the spatial QRS loop from mid-respiration (*1*, *2*) to inspiration (*3*, *4*).

Tables VII and VIII show, in a more quantitative way, the vectorial respiratory changes in various lead systems. In the conventional lead system and SVEC III, mean vectors were constructed from simultaneous time-based scalar leads. In the other lead systems as well as in SVEC III, the maximal vectors were determined from the scales of the SVEC machine. For SVEC III, therefore, both mean and maximal vectors were determined separately.

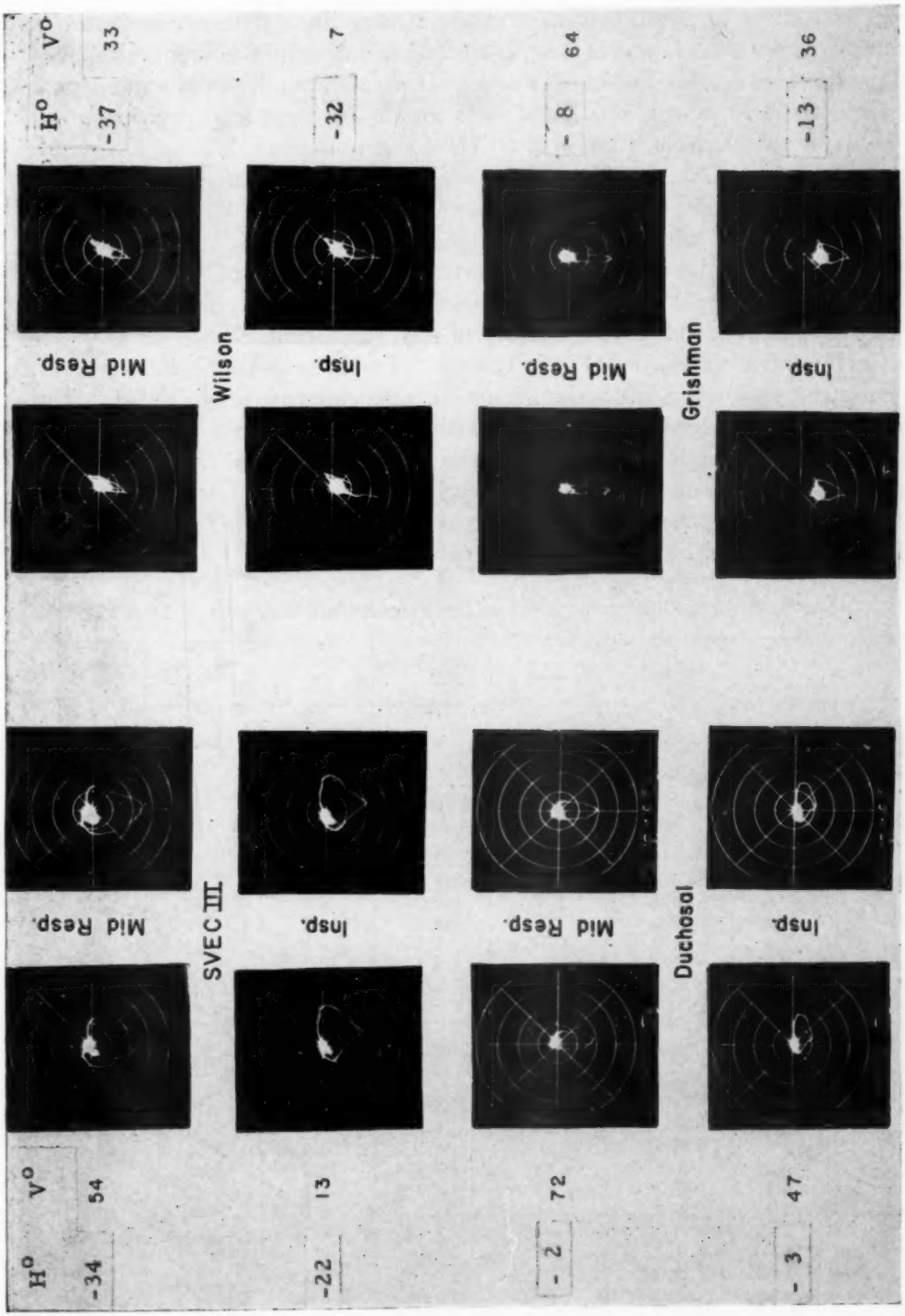


Fig. 7.—Spatial QRS vector loops which are recorded at their maximal extension with 4 different lead systems in one subject during mid-respiration and inspiration show differences in contour and orientation between the lead systems. The inserted figures for H° and V° indicate the degrees for the orientation of the maximal extension of the QRS loop in each record.

In all 4 subjects studied there were striking differences in direction and magnitude of QRS and T vectors between the different lead systems in all respiratory positions as well as in the respiratory changes, and these differences were not individually consistent. It was useless, therefore, to calculate the average changes for the group of subjects. Tables VII and VIII show the individual values for 2 of the subjects (A.M. and C.R.), Table VII for the 3 respiratory positions, and Table VIII for the changes from MR to IN ($\Delta 1$), and from MR to EX ($\Delta 2$).

In subject C. R., the backward movement of QRS-H° appears in all lead systems except the Wilson-Burch, which shows a pronounced forward rotation. This agrees, however, with Burch's findings and illustrates a limitation of this lead system. Briller's lead system shows a backward rotation of T-H°, while all other lead systems show a forward rotation (Table VIII). Subject A.M. is somewhat atypical because of the absence of any significant change of QRS-H° in SVEC III or the conventional lead system. The Wilson-Burch lead system, however, is the only one with a significant forward movement of QRS-H°, and the Briller system the only lead system with a backward movement of T-H°. The inscription of the QRS loop in the horizontal plane as seen from above was clockwise in the Briller system, and counterclockwise in the other lead systems. With these exceptions, the respiratory changes displayed in the several systems were in the same sense, but different in extent.

TABLE V. CLOCKWISE ROTATION QRS VECTOR GROUP VS. COUNTERCLOCKWISE ROTATION QRS VECTOR GROUP †

	QRS			T			dA°
	H°	V°	MAG.	H°	V°	MAG.	
Clockwise Rotation QRS Vector Group							
MR M	−51.2	42.3	6.63	53.2	56.5	3.93	74.3
S.D.	8.9	26.2	8.80	10.3	14.5	1.73	19.2
IN M	−60.0	32.8	8.30	60.2	55.7	3.17	74.7
S.D.	4.3	16.6	3.27	16.1	19.7	1.48	21.4
MΔ	− 8.8	− 9.5	2.17	7.0	− 0.8	−0.76	0.4
S.D. of Δ	6.8	12.7	—	8.1	12.6	—	17.3
t_{n-1}	3.184*	1.833	—	2.124	0.161	—	0.045
Counterclockwise Rotation QRS Vector Group							
MR M	14.4	44.8	12.01	51.0	60.0	4.16	36.4
S.D.	10.5	29.0	4.25	18.9	20.3	1.33	11.2
IN M	4.9	27.8	10.90	58.3	59.7	3.76	43.5
S.D.	12.4	18.1	4.63	19.4	15.7	2.21	9.8
MΔ	− 9.5	−17.0	1.11	7.3	− 2.1	0.40	7.13
S.D. of Δ	7.8	15.5	—	11.6	8.5	—	10.7
t_{n-1}	3.436*	3.111*	—	1.772	0.70	—	1.881
$t_{n1+n2-2}$	0.175	0.966	—	0.054	0.225	—	0.896
P_t	non sig.	non sig.	—	non sig.	non sig.	—	non sig.

†Code in Table III.
Statistical significance evaluated by the t-test: *P_t 0.05

TABLE VI. COMPARISON OF RESPIRATORY VECTORIAL CHANGES RECORDED WITH THE CONVENTIONAL LEAD SYSTEM AND SVEC III

ΔIN-MR	QRS						T						dA°	
	H°		V°		MAG.		H°		V°		MAG.			
	CONV.	SVEC III	CONV.	SVEC III	CONV.	SVEC III	CONV.	SVEC III	CONV.	SVEC III	CONV.	SVEC III	CONV.	SVEC III
	**	*	***	***		***	***	***	***	***			*	***
MΔ	−11.0	−7.6	−19.4	−9.4	−0.49	−1.60	11.4	15.6	−10.2	−5.0	0.05	0.14	5.9	16.8
S.D.	15.4	13.5	16.9	10.8	2.60	1.53	8.4	12.7	11.7	7.5	1.21	0.51	12.7	12.5
d	−3.4		−10.0*		1.11		−4.2		−5.2		−0.09		−10.9**	
Coefficient of Correlation	0.86**		0.52*		0.51*		0.45*		0.32		0.06		0.26	

d = MΔ CONVENTION − MΔ SVEC III.

Statistical significance evaluated by the t-test: * $P_t < 0.05$
** < 0.01
*** < 0.001

TABLE VII. SPATIAL QRS AND T VECTORS OF 2 SUBJECTS IN MR, IN AND EX, RECORDED WITH 8 DIFFERENT LEAD SYSTEMS*

LEAD SYSTEM CODE LETTERS	ITEM	SUBJECT A. M.							SUBJECT C. R.						
		QRS			T			dA°	QRS			T			dA°
	RESP.	H°	V°	MAG. (mm.)	H°	V°	MAG. (mm.)		H°	V°	MAG. (mm.)	H°	V°	MAG. (mm.)	
a	MR	−27	86	9.5	40	83	4.5	70	−32	10	10.0	20	32	1.7	27
	IN	−26	58	7.8	45	73	4.0	68	−44	13	10.1	55	22	1.8	28
	EX	−27	90	11.5	35	80	4.9	65	−32	15	7.4	15	33	2.0	26
b	MR	−16	75	16.4	31	76	5.4	44	− 9	30	14.9	33	49	3.4	31
	IN	−14	62	11.1	43	74	5.2	55	−28	32	13.0	70	46	4.6	57
	EX	−16	76	17.6	33	76	6.1	48	− 6	39	13.5	24	49	3.6	24
c	MR	−30	76	15.0	28	76	6.5	56	−12	55	18.5	14	53	6.0	23
	IN	−30	56	11.0	39	83	6.5	66	−56	44	17.5	36	53	4.5	66
	EX	−34	76	14.5	30	76	6.5	60	−12	56	18.5	8	53	6.0	18
d	MR	−44	62	14.0	16	66	5.0	54	−66	36	22.0	− 8	20	5.1	28
	IN	−66	53	14.0	37	54	4.0	78	−80	54	26.0	64	36	6.1	83
	EX	−45	74	16.0	10	57	4.5	52	−60	34	23.0	− 2	34	6.1	32
e	MR	−38	78	11.5	− 7	73	3.0	33	−22	46	14.0	0	37	4.3	20
	IN	−56	70	10.5	4	75	2.0	60	−66	44	13.0	60	40	3.5	73
	EX	−37	80	13.0	− 4	61	3.0	40	− 6	46	16.5	0	47	4.3	8
f	MR	−17	74	11.0	− 6	66	2.8	12	−20	39	15.0	5	36	3.5	18
	IN	−24	69	9.5	− 4	72	2.5	20	−44	32	13.0	10	28	3.2	26
	EX	−16	72	10.5	− 4	71	3.0	15	−13	35	15.0	4	39	4.0	13
g	MR	0	81	8.8	13	73	3.3	17	0	28	10.0	27	43	3.3	21
	IN	+10	57	6.3	17	67	2.8	11	+46	4	11.5	86	48	3.0	42
	EX	0	88	9.2	8	76	3.5	14	2	26	8.5	15	51	3.3	22
h	MR	− 7	79	6.5	−14	84	2.5	9	−10	44	8.0	−27	46	2.7	11
	IN	−24	58	5.0	−21	90	1.5	34	−20	10	10.0	−64	54	2.5	50
	EX	+ 2	80	8.0	−16	90	2.5	24	4	34	8.0	−20	44	3.0	17
i	MR	−15	64	16.0	35	78	6.5	51	−28	43	20.0	38	45	5.5	45
	IN	−25	64	13.5	35	73	6.0	56	−76	50	21.0	79	60	6.5	106
	EX	−15	77	17.0	35	73	6.5	50	−16	42	19.5	15	50	5.0	26

*Lead system code letters identified in Table VIII.

*Lead system code letters identified in Table VIII.

TABLE VIII. RESPIRATORY VECTORIAL CHANGES FROM MR TO IN (Δ1) AND FROM MR TO EX (Δ2) OF 2 SUBJECTS, RECORDED WITH 8 DIFFERENT LEAD SYSTEMS

LEAD SYSTEM CODE LETTERS		SUBJECT A. M.							SUBJECT C. R.						
		QRS			T			dA°	QRS			T			dA°
		H°	V°	MAG. (mm.)	H°	V°	MAG. (mm.)		H°	V°	MAG. (mm.)	H°	V°	MAG. (mm.)	
a	Δ1	+ 1	−28	−1.7	5	−10	−0.5	− 2	−12	3	0.1	35	−10	0.1	1
	Δ2	0	+ 4	2.0	− 5	− 3	0.4	− 5	0	5	−2.6	− 5	1	0.3	− 1
b	Δ1	+ 2	−13	−5.3	12	− 2	−0.2	11	−19	2	−1.9	37	− 3	1.2	26
	Δ2	0	1	1.2	2	0	0.7	4	3	9	−1.4	9	0	0.2	− 7
c	Δ1	0	−20	−4.0	11	7	0	10	−44	−11	−1.0	22	0	−1.5	43
	Δ2	− 4	0	−0.5	2	0	0	4	0	1	0	− 6	0	0	− 5
d	Δ1	−22	− 9	0	21	−12	−1.0	24	−14	18	4.0	72	16	1.0	55
	Δ2	− 1	12	2.0	− 4	− 9	−0.5	− 2	+ 6	− 2	1.0	6	14	1.0	4
e	Δ1	−18	− 8	−1.0	11	2	−1.0	27	−44	− 2	−1.0	60	3	−0.8	47
	Δ2	+ 1	2	1.5	3	−12	0	7	16	0	2.5	0	10	0	−12
f	Δ1	− 7	− 5	−1.5	2	6	−0.3	8	−24	− 7	−2.0	5	− 8	−0.3	8
	Δ2	1	− 2	−0.5	2	5	0.2	3	+ 7	− 4	0	− 1	3	0.5	− 5
g	Δ1	+10	−24	−2.5	4	− 6	−0.5	− 6	+46	−24	+1.5	59	5	−0.3	21
	Δ2	0	7	0.4	− 5	3	0.2	3	2	− 2	−1.5	−12	8	0	1
h	Δ1	−17	−21	−1.5	− 7	6	−1.0	25	−10	−34	2.0	−37	8	−0.2	39
	Δ2	9	1	1.5	− 2	6	0	15	14	−10	0	+ 7	− 2	0.3	6
i	Δ1	−10	0	−2.5	0	− 5	−0.5	5	−48	+ 7	1.0	41	15	0.5	61
	Δ2	0	13	1.0	0	− 5	0	− 1	+12	− 1	−0.5	−23	5	−0.5	−19

Lead system code letters: a: conventional (mean vector)
b: SVEC III (mean vector)
c: SVEC III (maximal vector)
d: SVEC II a
e: Duchosal-Sulzer
f: Grishman
g: Wilson-Burch
h: Briller
i: Frank

Having data both for mean and for maximum vectors in the SVEC III lead system, it becomes possible to compare these directly. The differences found can be ascribed to the different segments of the loop represented in the mean and maximum vectors, which is illustrated in Figs. 6 and 7 for subject R.J.

Table IX lists for each of the 4 subjects the extreme angular positions of vectorial axes found among any of the different lead systems and identifies that system giving these extreme values. The differences in MR position and in the changes from MR to IN (Δ1) are tremendous, more so for H° than for V°. In 3 of the 4 subjects, the Wilson-Burch lead system (*g*) shows the extreme forward orientation of QRS-H° in MR and Δ1, and the Briller system (*h*) shows the extreme values of inspiratory posterior rotation of T-H° in all 4 subjects. This is opposite in direction to the other systems.

System *g* also shows the smallest dA° in Δ1 in 3 subjects, and is opposite in direction to the other systems (a decrease instead of increase). System *i* (Frank) shows the largest dA° (an increase) in 2 subjects.

Part 3: Quantitatively Fractionated Respiratory Effects.—

The material presented thus far, as well as that in all previous studies, is qualitative in the sense that the volume of the respiratory changes was not controlled. This may account for a large part of the individual differences, since the maximal inspiration or expiration depends on individual cooperation and vital capacity.

TABLE IX. EXTREMES OF THE VECTORIAL ANGLES IN MID-RESPIRATION (MR) AND CHANGES FROM MID-RESPIRATION TO INSPIRATION (Δ1) IN 4 SUBJECTS, RECORDED WITH 8 DIFFERENT LEAD SYSTEMS

	ITEM	QRS-H°		QRS-V°		T-H°		T-V°		dA°	
	SUBJECT	ANT.	POST.	SUP.	INF.	ANT.	POST.	SUP.	INF.	LARGE	SMALL
MR	A.M.	0	−44	86	62	40	−14	84	66	70	9
	System	g	d	a	d	a	h	h	d,f	a	h
	C.R.	0	−66	46	10	38	−27	49	20	45	11
	System	c, g	d	c, e	a	i	h	b	d	i	h
	M.B.	26	−44	60	24	42	4	73	40	49	15
	System	g	d	e	d	a	f	f	d	a	e
	R.J.	− 2	−37	72	23	42	−11	76	40	57	10
	System	e	g	e	a	a	d	c	a	b	d
Δ1	A.M.	+10	−22	0	−28	21	− 7	7	−12	27	− 6
	System	g	d	i	a	d	h	c	d	e	g
	C.R.	+46	−48	18	−34	72	−37	16	−10	61	1
	System	g	i	d	h	d	h	d	a	i	a
	M.B.	0	−29	0	−18	28	− 6	17	− 4	32	0
	System	c, e, g	i	c, d, g	f	a	h	d	g	i	g
	R.J.	+12	−56	4	−40	43	−20	6	−35	39	−16
	System	c	h	a	h	b	h	e	g	b	g

Lead system code letters identified in Table VIII.

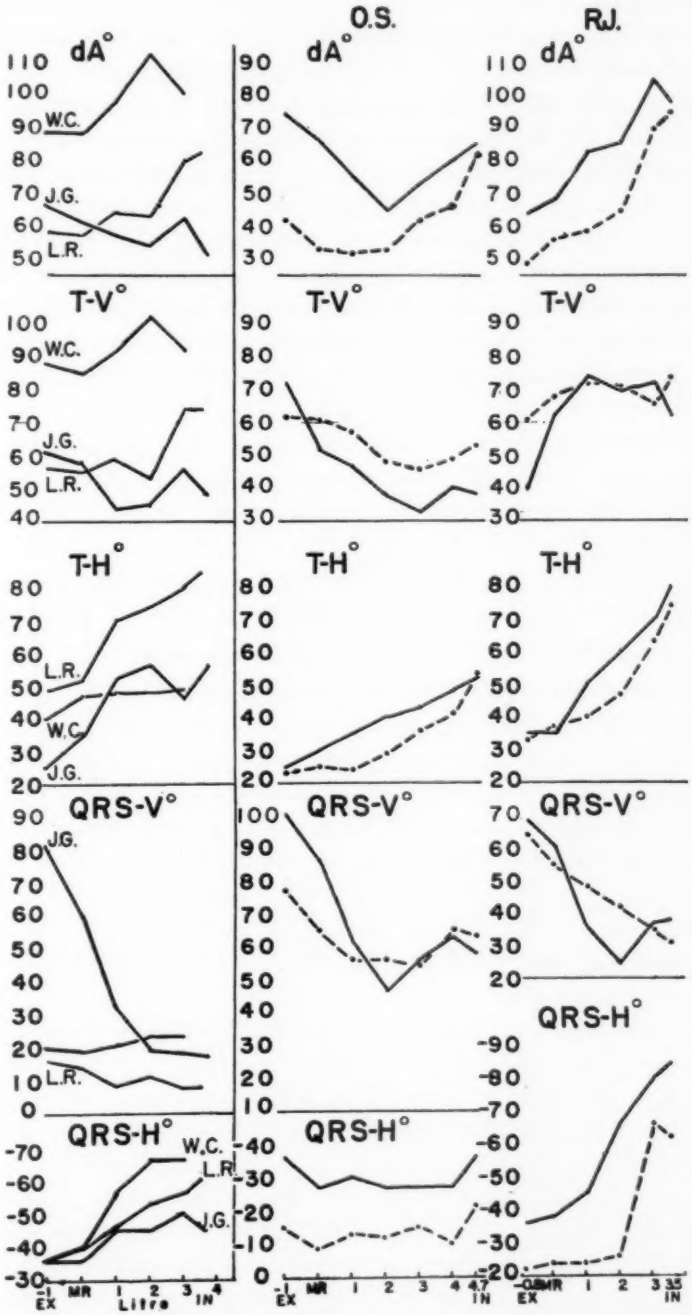


Fig. 8.—Fractionated respiration. The whole range of vital capacity in 1,000 c.c. fractions is shown on abscissa. The left column shows the axes of mean QRS and T vectors, constructed for 3 subjects (J.G., W.C., and L.R.) from the conventional lead system. In the central and right columns, the conventional lead system and SVEC III are compared in 2 subjects (O.S. and R.J.).

We determined the respiratory changes in 1,000 c.c. fractions over the whole range of vital capacity, zero being taken as mid-respiration. Fig. 8 shows the vectorial axes as a function of respiratory volume. In the left column are shown the results for 3 subjects using the conventional lead system. In the central and right columns are the values for 2 subjects (O.S., R.J.), determined with the conventional and SVEC III lead system. Subjects L.R. and W.C. have vertical hearts and show little change of QRS-V°, but greater changes of QRS-H°.

The changes do not approach linearity except for QRS-H° in L.R., and T-H° in O.S., both with the conventional lead system. The pattern of changes in the 2 lead systems is very similar for both O.S. and R.J., in spite of considerable absolute differences in some of the items, for instance QRS-H°. As a significant interindividual correlation was found for most items between the 2 lead systems, the similarity of the patterns of respiratory changes in the 2 lead systems for one individual is not surprising.

The individual differences of vectorial changes cannot be ascribed merely to individual differences in the respiratory volume, as they also appear when subjects having different vital capacities are compared at the same inspiration or expiration volume. It should be noted that the scales for T-H° are positive, while those for QRS-H° are negative, indicating opposite direction.

The results shown in Fig. 8 are also incompatible with anatomic positional changes as the sole basis for respiratory vectorial changes.

Part 4: Respiratory Axis Shifts in Bigeminy.—

In 4 subjects having ventricular bigeminy with normal regular conducted beats, it was possible to record simultaneously, but separately, the respiratory

TABLE X. CHANGES OF MEAN QRS AND T VECTORS, RECORDED WITH DIFFERENT LEAD SYSTEMS, FROM MID-RESPIRATION TO DEEP INSPIRATION, IN REGULAR AND PREMATURE VENTRICULAR BEATS

SUBJECT	LEAD SYSTEM	BEAT	QRS			T			
			H°	V°	MAG. (mm.)	H°	V°	MAG. (mm.)	dA°
R.L.	Conventional	regular	− 6	−10	−2.7	12	− 2	−0.7	22
		premature	15	− 6	−9.1	− 9	− 6	−2.0	−10
	SVEC II b	regular	−17	− 7	−2.1	− 4	− 1	−2.2	13
		premature	4	− 9	−5.7	8	− 5	−1.8	−18
G.B.	SVEC III	regular	− 3	4	0.6	14	− 6	−0.1	8
		premature	− 4	9	−5.8	15	−19	−0.6	−16
H.N.R.	Conventional	regular	− 5	−15	0.1	0	−18	0.1	−19
		premature	− 6	−42	−1.0	18	16	0.5	25
	SVEC III	regular	− 2	− 7	−2.0	0	0	0	0
		premature	− 4	− 8	0.9	6	17	−1.6	−10
H.R.	SVEC III	regular	− 4	12	−2.8	2	− 2	−0.2	16
		premature	−16	7	2.5	8	6	0.3	2

changes of mean QRS and T vectors in the regular and in the premature ventricular beats. Markedly different respiratory effects were seen between regular and premature beats in all subjects in each of the 3 lead systems used in this series (Table X). We must stress the large respiratory differences between regular and premature beats of the vector magnitude and dA° in the presumably correct lead system SVEC III where these items should be independent of position. The changes of QRS-Mag. between regular and premature beats are opposite in direction in 3 of the 4 subjects, G.B., H.N.R., and H.R. In the the total of 6 comparisons, 5 show opposite directional changes of dA°: the dA° of the regular beats tending to increase, that of the premature ventricular beats tending to decrease with deep inspiration. We must think that the discrepancies between regular and premature beats in the respiratory changes of mean QRS and T vectors cannot be adequately explained on the basis of positional changes.

DISCUSSION

In contrast to the generally accepted opinion, the electrocardiographic changes associated with respiration cannot be explained by positional changes alone. In many subjects the vectorial changes are too large, particularly in the horizontal plane; the azimuth (H°) of QRS and that of T move in different directions. Although the elevational changes of QRS-V° and T-V° are concordant, their extents are very different. Changes of vector magnitude and dA° which are position independent are frequently found, and individual differences also appear at the same volume of inspiration or expiration. The vectorial shifts with changing respiratory volume are not, in general, linear.

The vectorial respiratory changes of regular and premature ventricular beats are markedly different, and changes of the loops produced in maximum inspiration influence the mid-respiratory patterns for many seconds after return from inspiration. An interesting parallel to these persistent changes is found in Mayerson's[26] observations on electrocardiographic changes produced by tilting from supine to upright position. These, too, can hardly be explained by positional changes alone.

Although vagal effects on the ventricular complexes are slight or absent in animal experiments, this possibility, we felt, should not be ruled out. In exploratory experiments on 2 subjects, however, atropine did not affect the respiratory vectorial changes. Hemodynamic factors are probably involved, but the detailed mechanism needs further exploration. It is anticipated that investigation of a substantial number of patients with established cardiac pathology types may contribute to elucidation of the mechanisms involved. Such a series is in progress.

Certainly, the respiratory position should be considered in the ordinary electrocardiographic routine. The range of angular axis position found in normals in mid-respiratory position is so large (127.5°)[27] that this item does not lend itself well to differentiation between "normal" and abnormal subjects. In deep inspiration there is a much narrower axis range, so that even a moderate axis shift in abnormals could be of diagnostic significance.

The differences of initial vector directions and magnitudes, as well as the shifts associated with respiratory changes for different lead systems, are sur-

prisingly large. These effects are presumably due to differential distortion of the various leads in recording contributions from different parts of the heart.

The differences in loop configurations for various lead systems on the same individuals were demonstrated in Fig. 7. It is important that the large differences are apparent not only in mid-respiration, but also in the intraindividual respiratory changes. In former studies we found significant correlations, in spite of significant differences, between vectors obtained from the conventional and from the SVEC II lead systems.[21] In this series we found this also to be true for the SVEC III system. It is not obvious that this correlation would also exist for other lead systems and, consequently, this relationship for various other lead systems needs experimental confirmation. It is understandable that appreciably different vector values will be found by mean vector and by maximal vector measurements even on identical subject data taken with identical leads, for somewhat different segments of the loops will establish the vector directions and magnitudes in the two cases.

The results stress the need for lead system standardization in vectorcardiography: without such standardization, confusion and conflicting results are inevitable. We must not, however, hide real defects in lead system performance by mere arbitrary standardization.

SUMMARY

1. In 38 normal men, there was a statistically highly significant inspiratory backward rotation of the mean QRS vector and forward rotation of the T vector as constructed from conventional leads with a mechanical vector analyzer, and opposite, though smaller, changes in maximal expiration.

2. The downward movement of the mean QRS vector in maximal inspiration exceeded that of the T vector.

3. The average respiratory changes of the vector magnitudes were statistically not significant, but in some subjects the changes were large.

4. The angle between the spatial QRS and T vectors increased significantly in inspiration.

5. There was a significant correlation between mid-respiratory position and respiratory changes in the elevation, but not in the azimuth of the vectors.

6. Age was not found to affect the respiratory vectorial changes.

7. The respiratory changes of mean QRS and T vectors, constructed from the conventional leads and from the electrically orthogonal X, Y, Z leads of the SVEC III system, in 22 men, were in the same direction but different in extent. The interindividual variability was large in both lead systems.

8. In 4 men, the respiratory changes of spatial QRS and T loops were oscillographically recorded with 7 different lead systems (SVEC IIa, SVEC III, Briller, Duchosal, Frank, Grishman, and Wilson-Burch).

9. Discrepancies between respiratory changes of QRS and T vectors were noted in all lead systems investigated. Changes of spatial loop configurations were also seen in all systems.

10. The differences of vector orientation and magnitude between the several lead systems, both in regard to the initial mid-respiratory position and to the

respiratory changes, in each of the subjects, were tremendous, the extremes exceeding the biologic variability. One lead system (Wilson-Burch) showed a change of the QRS vector opposite in direction to that in all other lead systems.

11. In 5 subjects, the spatial vectors were studied over the whole range of vital capacity in fractionated respiration. It was proved that variations in vital capacity do not account for the large interindividual differences that were found.

12. In 4 patients with ventricular bigeminy, the vectorial respiratory changes of the normal regular and the premature ventricular beats were different.

13. The experimental results cannot be explained adequately on the basis of anatomic respiratory changes alone.

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Clinical Report

MITRAL REGURGITATION DUE TO RUPTURED CHORDAE TENDINEAE CORRECTION BY "MITRAL PURSE-STRING"

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IN A group of 43 consecutive patients studied with a view towards surgery for correction of mitral insufficiency, 4 were found to have ruptured chordae tendineae. Two of these did not have surgical intervention and died. The third was a case with rheumatic heart disease resulting in the rupture of two chordae tendineae. Inversion of the wall of the atrium to enhance approximation of the valve cusps in the region of the posteromedial commissure with a mattress suture was attempted unsuccessfully elsewhere. A second operation was performed in this hospital but uncontrollable hemorrhage and cardiac arrest resulted in the death of the patient. Necropsies were performed in these 3 cases and the specimens were studied on the pulse duplicator.[1]

TABLE I. ROENTGENOGRAPHIC ANALYSIS OF CARDIAC CHAMBER SIZE*
(COMPARISON OF PREOPERATIVE AND POSTOPERATIVE FINDINGS)

SITE	PREOPERATIVELY	3 MO. POSTOPERATIVELY	9 MO. POSTOPERATIVELY
Pulmonary Artery	4+	2+	2+
Branch Vessels	1+	1+	1+
Aorta	2+	2—3+	2—3+
Right Atrium	4+	2+	2+
Right Ventricle	4+	2—3+	2—3+
Left Atrium	3+	2—3+	2—3+
Left Ventricle	2+	1+	1+
Perimeter adjusted to mirror the volume (in arbitrary units)	3,100	2,784	2,850

*Based on grading of 1 to 4.

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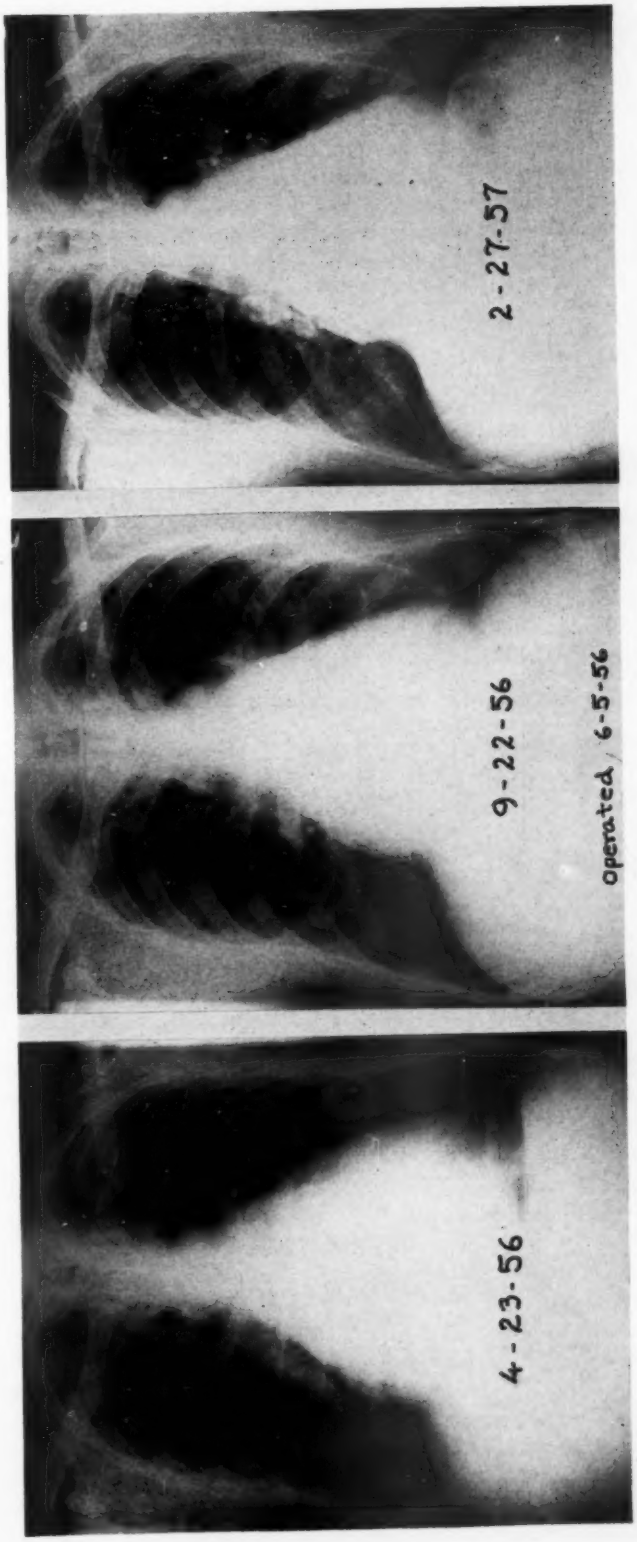

Fig. 1.—Comparison of posteroanterior teleroentgenograms taken 3 months preoperatively, and 3 and 9 months postoperatively. The decrease in cardiac size is evident.

The fourth case was that of J. S., a 55-year-old sheet metal worker who entered the hospital complaining of dyspnea. He said that he was born with a heart condition and had received treatment for many years. He had no knowledge of rheumatic or scarlet fever. In October 1955, congestive failure manifested itself by the onset of edema and cough. In January 1956, he developed hemoptysis and complete intolerance of exertion requiring hospitalization. It became increasingly difficult to maintain him in comfort and out of failure on a regimen of digitalis, mercurials, salt-free diet, and rest. When he was referred for surgical evaluation he was totally incapacitated by intractable congestive failure.

On physical examination he was afebrile, had a blood pressure of 150/100 mm. Hg, and was in atrial fibrillation with an apical rate of 80 to 90 per minute. The heart was markedly enlarged to

TABLE II. HEMODYNAMIC DATA
(COMPARISON OF PREOPERATIVE AND POSTOPERATIVE FINDINGS)

SITE	3 MO. PREOPERATIVELY (APRIL 27, 1956) WEIGHT—134 LBS.		9 MO. POSTOPERATIVELY (FEB. 26, 1957) WEIGHT—153 LBS.	
	PRESSURES (MM. Hg)	O_2 VOL. %	PRESSURES (MM. Hg)	O_2 VOL. %
PVC				
rest	60/20 (29.8)		40/14 (23)	
exercise	*		60/20 (38)	
P.A.				
rest	64/32 (49)	8.92	50/25 (33)	13.24
exercise	*		72/35 (50.7)	11.41
R.V.	68/8 (29.7)	8.84	50/4 (24.8)	
R.A.	13.5/10 (12.5)	9.35	12/6 (8.6)	
Arterial				
rest	116/74 (femoral)	16.49 (90% sat.)	148/84 (brachial)	18.81 (93% sat.)
exercise	*		160/88 (brachial)	18.15 (90% sat.)
Cardiac Output				
rest	2.05 L./min.		3.91 L./min.	
exercise	*		9+ L./min.	
Pulmonary Vascular Resistance	1,760 dynes/sec./cm.$^{-5}$		680 dynes/sec./cm.$^{-5}$	
A-V O_2 diff. at rest	7.14 — 7.57		4.57	
Left Atrial Puncture (transbronchial)	85/22 (35)		60.20 (28)	

Direct Puncture at Surgery

	BEFORE	AFTER
L.A.	78/16	18/5
L.V.	108/16	120/5
End-diastolic	12	6
Aorta	108/68	120/80

Figures in parentheses are mean pressures.
*Exercise test not deemed advisable in view of patient's condition.

the left with the apex in the seventh intercostal space at the anterior axillary line. There was a Grade 4 apical systolic murmur which was transmitted over the entire precordium and towards the axilla. An opening mitral snap and a systolic thrust and thrill were also appreciated at the apex. The pulmonary second sound was greatly accentuated. There were moist râles in the right base. The liver was enlarged 4 fingerbreadths below the costal margin, nontender and firm. The spleen was similarly enlarged 1 fingerbreadth. He had 1 plus pitting edema of the extremities.

Routine laboratory examination revealed only a mild anemia with a hemoglobin of 12.8 Gm. Roentgen examination revealed a "mitral" configuration of the heart with enlargement of all the cardiac chambers (Table I and Fig. 1). The electrocardiogram showed combined ventricular hypertrophy and strain as well as digitalis effect. Right heart catheterization and transbronchial left atrial puncture revealed the data given in Table II and Fig. 2.

On June 5, 1956, at operation, the following findings were noted. The left atrium was enlarged 4 plus, being almost aneurysmal. The right ventricle, pulmonary artery, and pulmonary veins were enlarged 3 plus, while the left ventricle was enlarged 2 plus. There was a very prominent systolic thrill over the left atrium, pulmonary veins, and even into the lung substance. Upon digital examination through the left atrial appendage, massive regurgitation was found throughout the length of the valve orifice. Very little of the mural leaflet remained. This structure was contracted but retained a little pliability. The aortic leaflet was somewhat contracted and tense but retained considerable pliability. One or two of the chordae tendineae of the medial side of the aortic leaflet of the mitral valve were ruptured and this portion of the leaflet was flailing in the blood stream during both systole and diastole. The mitral ring was dilated to about 5 fingerbreadths and the effective mitral orifice was about 3 fingerbreadths wide. No calcification was evident. The chordae tendineae were short and thick. Intracardiac pressures measured by direct puncture are given in Table II.

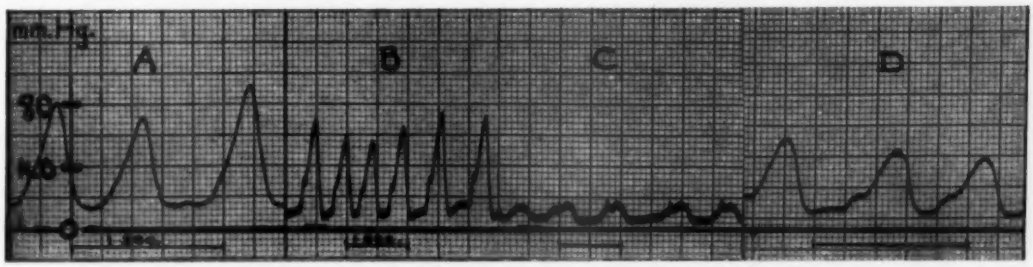

Fig. 2.—Left atrial pressure pulse tracings. *A*, Transbronchial puncture 3 months preoperatively. *B*, At surgery before correction. *C*, At surgery after correction. *D*, Transbronchial puncture 3 months postoperatively.

In veiw of the above findings, mitral circumferential suture[2,3,4] was undertaken. As the "purse-string" was slowly tied down, the mural and aortic leaflets could be felt to coapt. The mitral ring was brought down to a diameter of about 3 fingerbreadths while the effective orifice remained unaffected. The aortic leaflet could now be felt to coapt with the mural leaflet and perhaps overlap a little. Although a regurgitant jet was still palpable, this was greatly diminished in magnitude and localized to the central portion of the valve. The previously tense and distended left atrium was now quite flaccid. It was only with difficulty that a faint systolic thrill could be appreciated over the posterolateral aspect of the atrium. Direct intracardiac pressure measurements were repeated (Table II).

The postoperative convalescence was uneventful. Three months later he was clinically much improved. He could climb stairs and walk 4 blocks without dyspnea. He did have occasional mild ankle swelling. There was a Grade 2 to 3 systolic murmur over the mitral area which was transmitted faintly to the axilla. Roentgen examination showed diminution in the size of the heart. The changes are noted in Fig. 1 and Table I. In the electrocardiogram the left ventricular

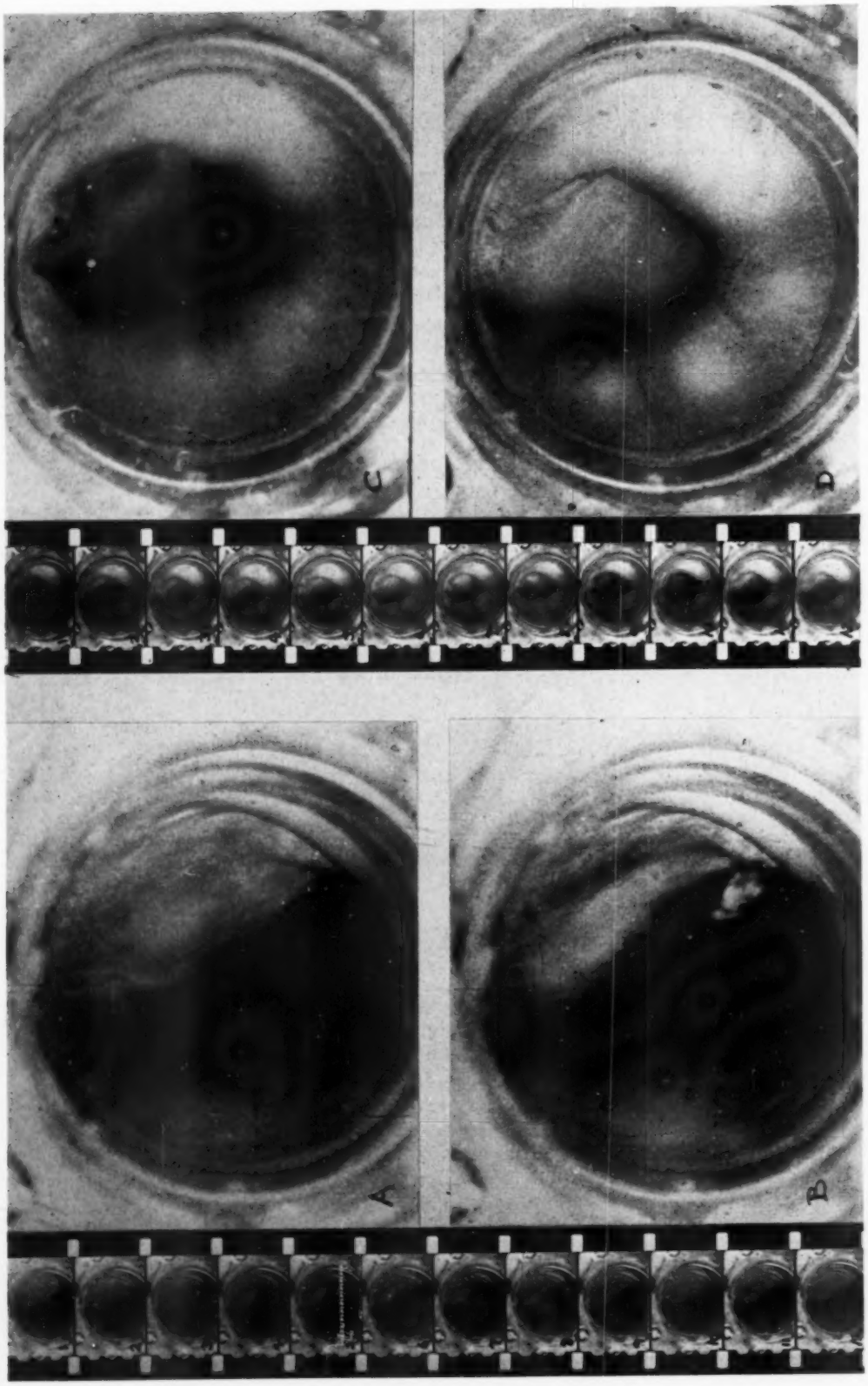

Fig. 3.—Mitral valve action in specimen from a patient who died within 1 year of appearance of a loud apical systolic murmur following an episode of subacute bacterial endocarditis. Note the stumps of two ruptured chordae seen in systolic phase (frames 2 to 6 on film strip). *A*, Valve seen in mid-diastole (maximum retraction in uncorrected state). *B*, Valve in systole (maximum coaptation in uncorrected state). *C*, Valve in mid-diastole (maximum retraction in corrected state); the effective orifice will admit 2 to 3 fingers. *D*, Valve in systole (maximum coaptation in corrected state) closes tightly.

leads showed increased voltage, a little further depression of the S-T segment, and consistently negative T waves, persistent left ventricular hypertrophy, and somewhat increased left ventricular strain. The transbronchial left atrial pressure at this time had increased but remained considerably below the preoperative value (Table II and Fig. 2).

Nine months after operation the patient was called back for further examination and study. He stated that he had been well. He gained 19 pounds. No dyspnea or orthopnea were noted. One month before this interview, at a party, he was able to climb 3 flights of stairs twice without dyspnea. No history of ankle edema was elicited. The diminution in cardiac size on roentgenograms had persisted (Fig. 1 and Table I).. The electrocardiogram showed better voltage in all leads, definitely less evidence of left ventricular hypertrophy and strain than in the tracing made 3 months postoperatively and possibly a little better than in the preoperative tracing. Right heart catheterization was performed and the findings are summarized in Table II.

The rather remarkable clinical improvement in this previously intractable case is substantiated by the hemodynamic data. In this regard the following points are of particular interest: increased cardiac output with notably marked increase during exercise; decreased pulmonary vascular and arterial oxygen saturation at rest; rise in arterial systolic and diastolic pressure; and decrease in all right heart pressures.

Although 58 cases with mitral regurgitation resulting from rupture of cardiac papillary muscle or chordae tendineae have been reported in the medical literature,[5,6] none were treated surgically. In all but a few the lesion was fatal within hours. An occasional patient survived several months. The most common etiology was myocardial infarction; however, endocarditis, sepsis, syphilis, and periarteritis accounted for some.

In only 1 of the 4 patients mentioned in this report was the etiology of the lesion clearly apparent. This man had subacute bacterial endocarditis 9 months before his death. One patient, the third case noted, had a history of rheumatic fever. In the others, none of the available information suggested the etiology of the rupture of the chordae.

The rapid and dramatic succession of events following onset of this lesion is well known. In those cases in which myocardial infarction is the cause of papillary muscle rupture, the acute and extensive myocardial injury probably renders surgical intervention of value in few, if any, instances. On the other hand, in those in whom endocarditis, whether rheumatic or bacterial, causes rupture of the chordae, surgery may be lifesaving.

That this type of mitral regurgitation can be corrected by circumferential suture of the mitral annulus has been shown in the case here presented. Further conclusive evidence of this is the demonstration of the mechanical efficacy of this technique in the 3 post-mortem specimens of the other cases. These were studied on the pulse duplicator. Cinematographic records of the action of the valves before and after the purse-string operation are reproduced in Fig. 3.

SUMMARY

Four cases of mitral insufficiency due to ruptured chordae tendineae have been seen in a group of 43 patients studied.

One case in which surgical correction led to an excellent clinical result is presented with objective data to substantiate the clinical impression.

Three specimens were studied on the pulse duplicator, showing the mechanical efficacy of the technique.

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Announcements

THE ALBERT EINSTEIN MEDICAL CENTER will conduct a POST-GRADUATE COURSE IN ADVANCED ELECTROCARDIOGRAPHY at the Southern Division, Fifth and Reed Sts., Philadelphia 47, Pa., beginning Feb. 19, 1958. The course will consist of a total of 30 hours of instruction divided into 10 sessions of 3 hours each. The sessions will be held on consecutive Wednesdays from 2 to 5 P.M. The fee for the course is $50.

The ELEVENTH ANNUAL MEETING of the WESTERN SOCIETY FOR CLINICAL RESEARCH will be held Thursday afternoon and Friday and Saturday mornings, Jan. 30 through Feb. 1, 1958, at Carmel-by-the-Sea, California.

Information regarding the meeting may be obtained from Arthur J. Seaman, M.D., Secretary-Treasurer, Western Society for Clinical Research, University of Oregon Medical School, Portland 1, Oregon.

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[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Medicine and Clinical Therapy, 3:322, October 1956.

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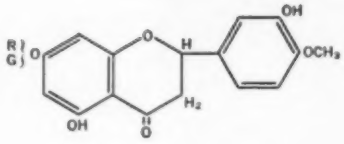

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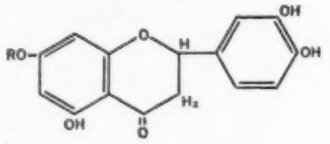

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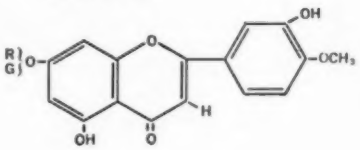

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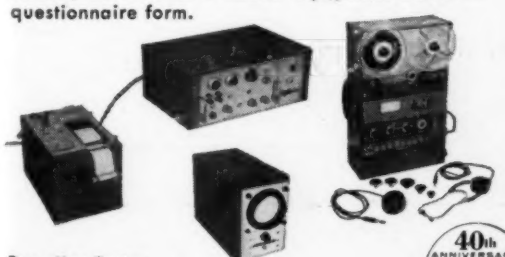

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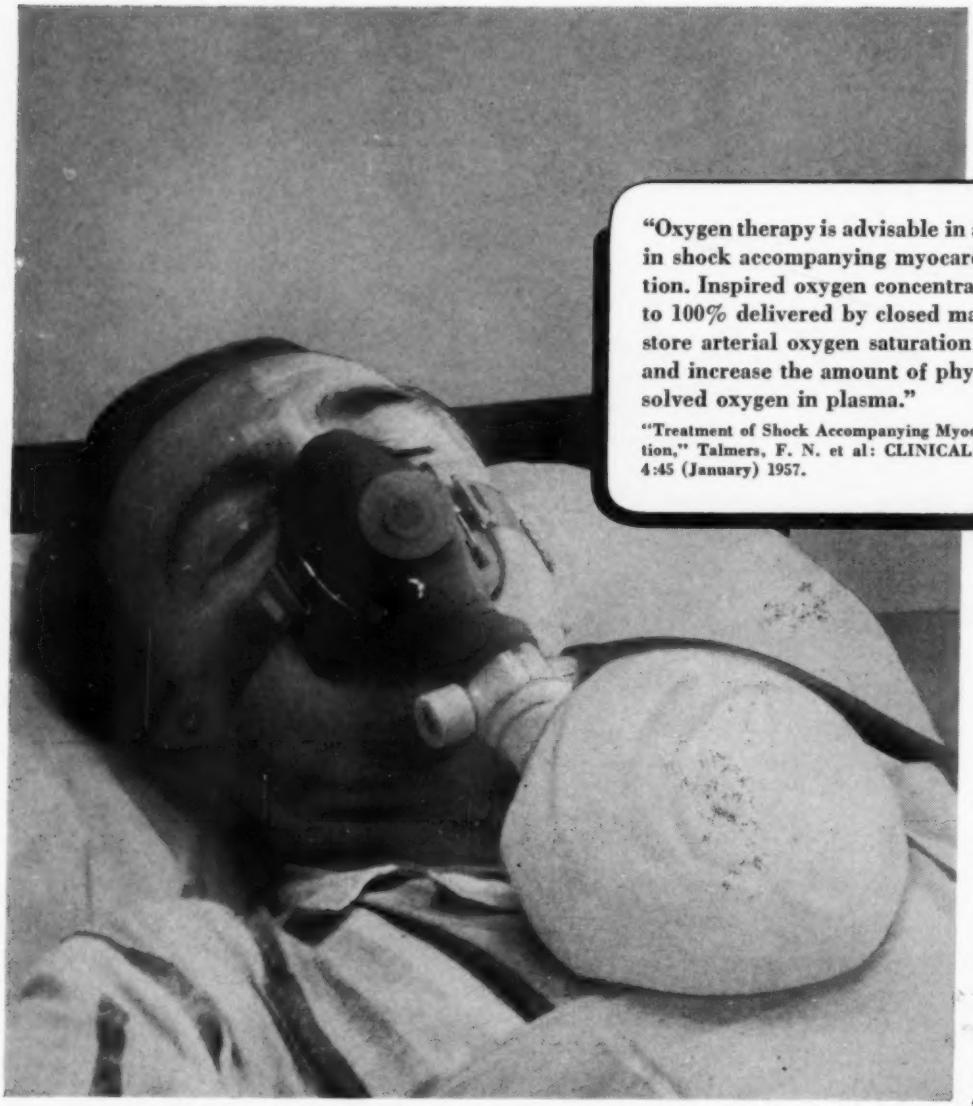

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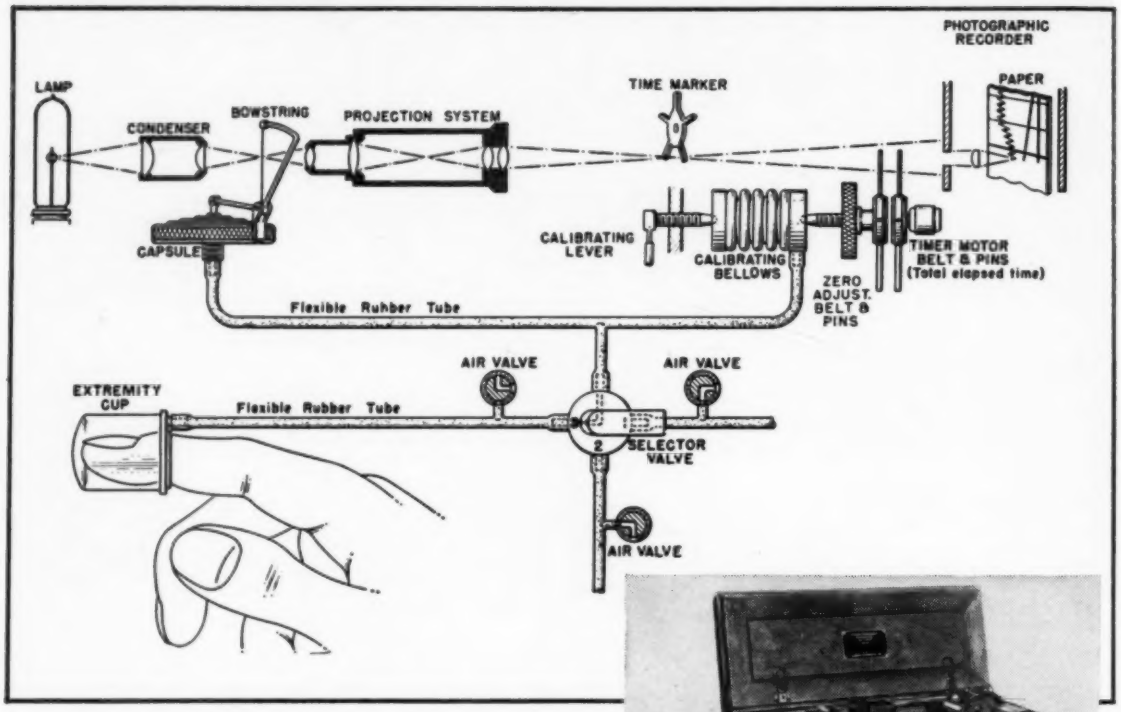

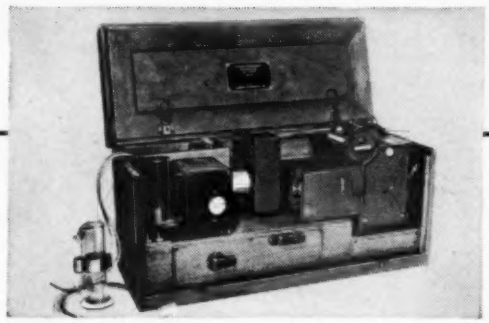

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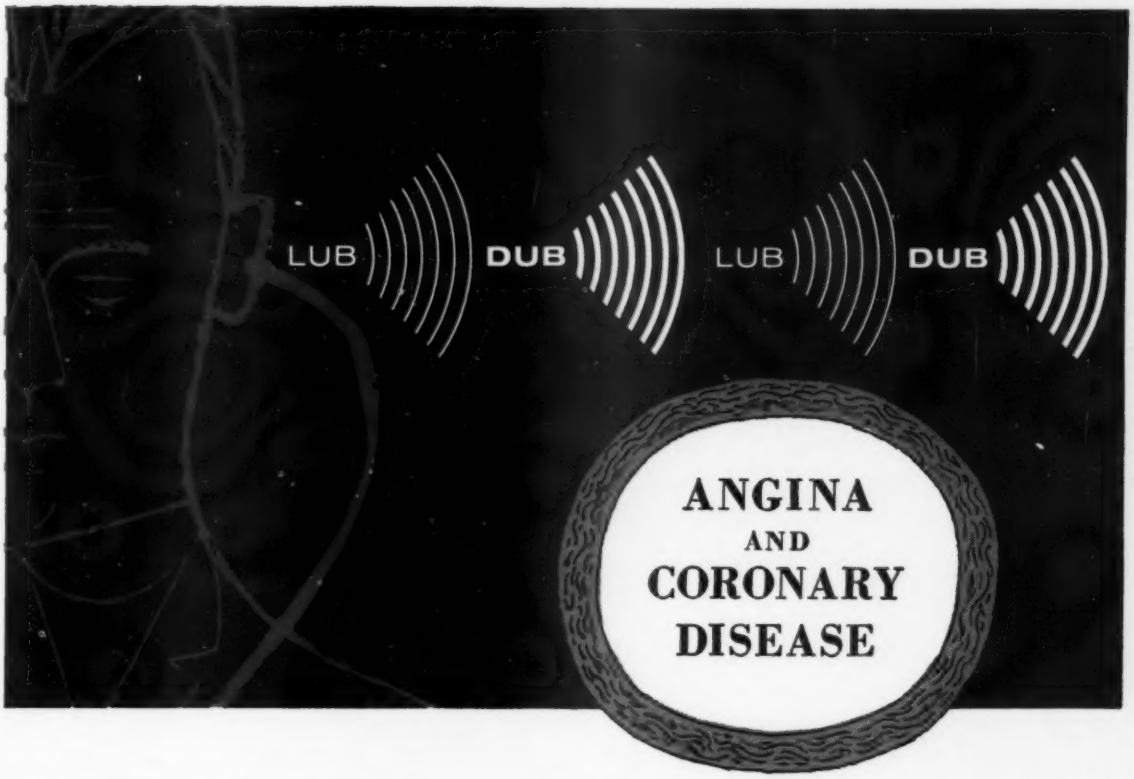

The Value of Blood Cholesterol Regulation

Studies[1-4] indicate that atherosclerosis is the underlying disease process in 80-90% of Americans who had myocardial infarction or angina with abnormal EKG patterns. It is also known that patients with coronary disease frequently have elevated blood cholesterol levels.

In these studies[1-4] patients with coronary occlusion "felt better" when their blood cholesterol was reduced by diet and a special cholesterol lowering formula. Anginal symptoms abated and none had a new coronary occlusion while on this therapy.

Patients with anginal attacks treated by Schroeder[5] with a high essential fatty acid and B_6 diet noted considerable lessening of anginal attacks.

Van Gasse and Miller[6] report marked pain relief by angina patients while on linoleic acid and B_6 medication. They recommend this formula for patients with high cholesterol levels, coronary thrombosis or angina.

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The preponderance of evidence indicates that all persons who have elevated blood cholesterol (with or without clinical evidence of disease) . . . and all persons with a condition associated with atherosclerosis (even though blood cholesterol is normal) are candidates for a cholesterol regulation program.

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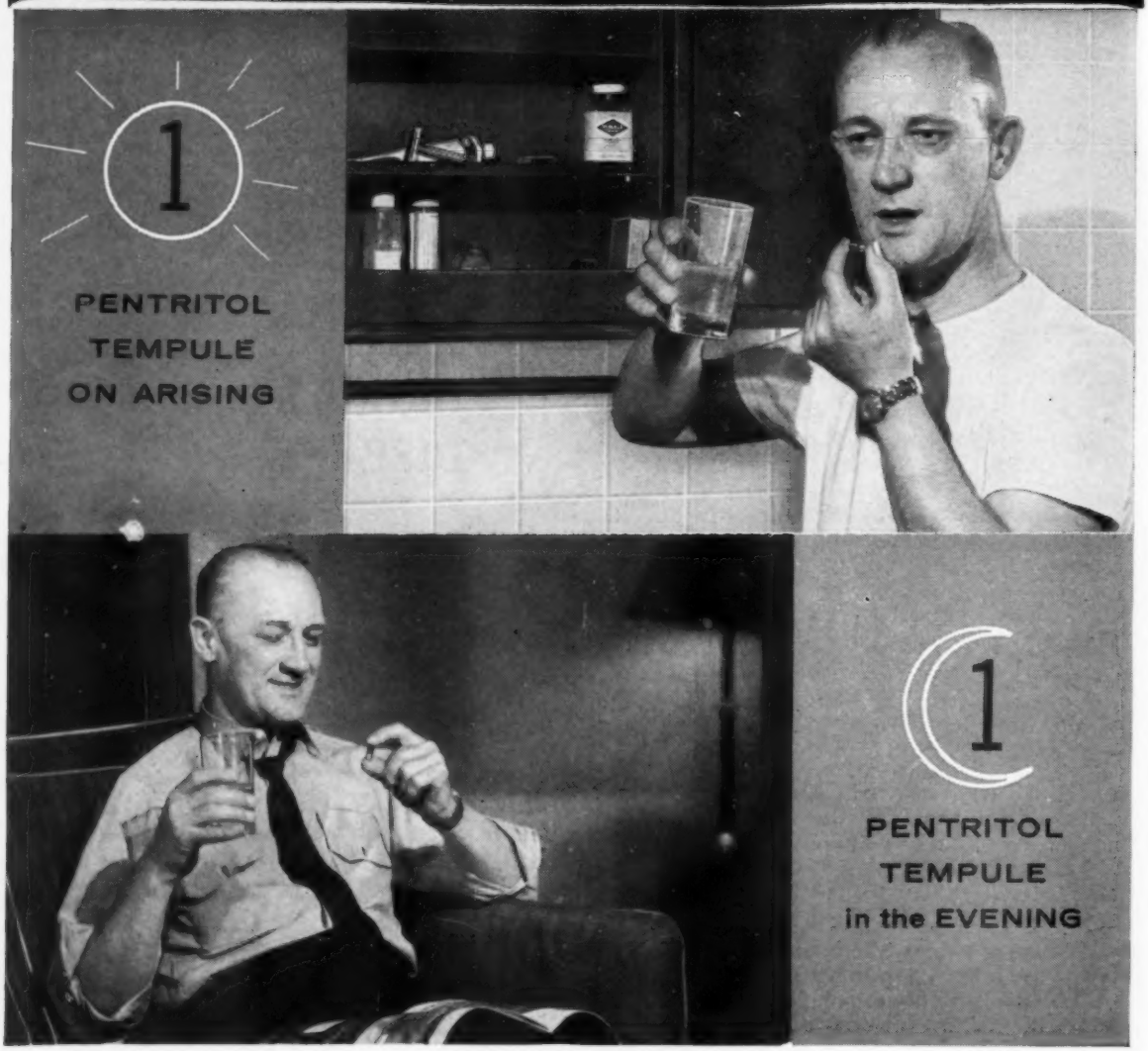

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These results show the effectiveness of Pentritol's 24-hour vasodilation.

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1. No tissue sloughs, necrosis or thrombophlebitis reported[1]
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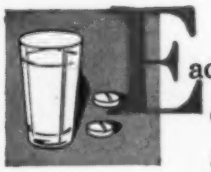

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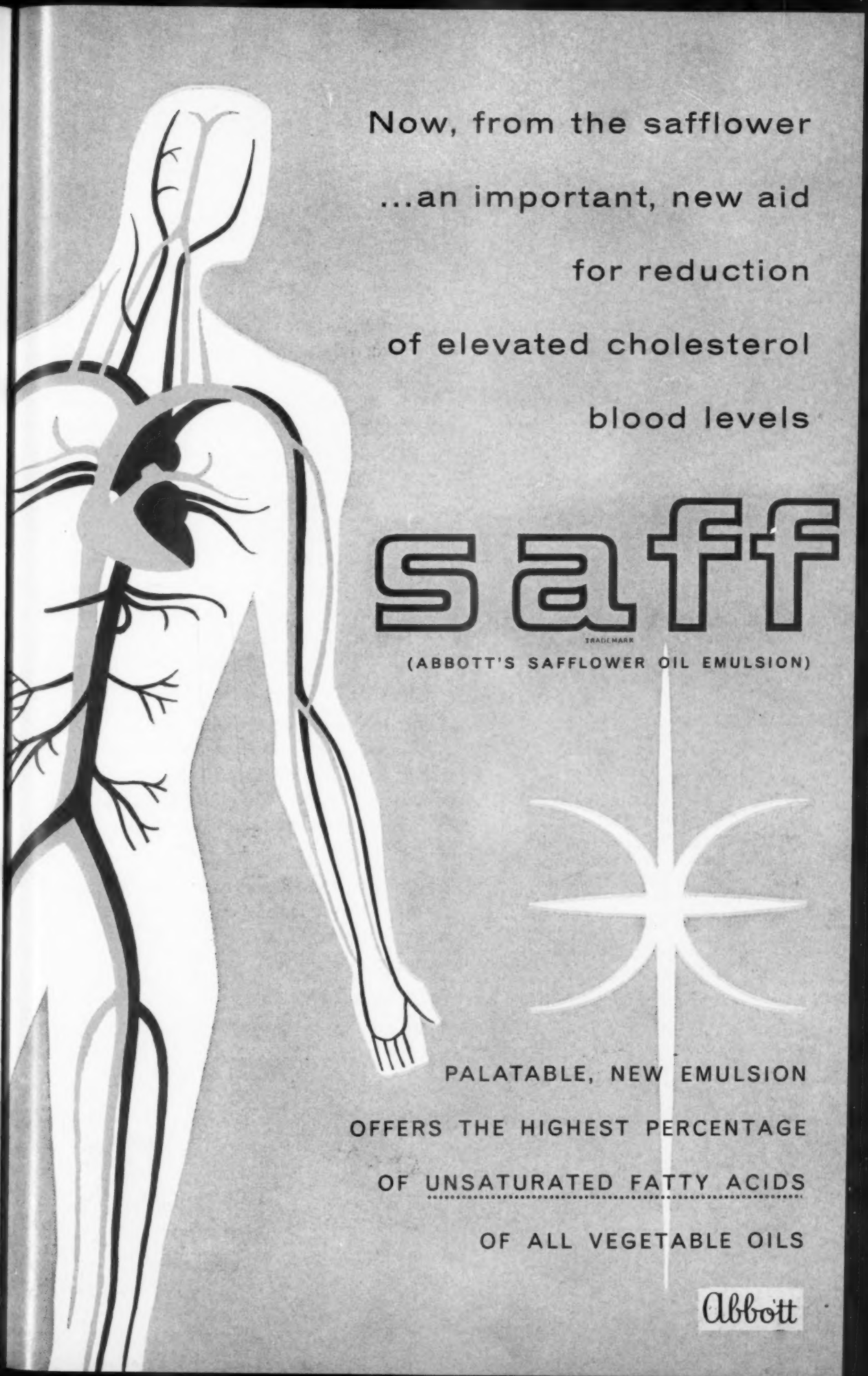
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What is a Sensible Breakfast?

The division of his day into periods for productive work, for play, and for sleep makes man fare best when his total daily food intake is distributed over three sensibly organized meals.

Since a high percentage of adolescents and adults forego or skimp breakfast, the physician might well point out the need for a sensible breakfast: a meal which provides energy for a morning of productive work, which allays hunger until the noon meal, which supplies an adequate share of the day's nutrient requirements, and which consists of inviting, easily digested foods.

A dish of oatmeal helps fulfill the requirements of such a breakfast: It provides readily available energy; it helps to allay hunger throughout the morning; it makes a notable contribution to the day's nutritional needs; it fits into virtually every breakfast, including most of those especially low in calories.*

Oatmeal is richer in protein than other whole-grain breakfast cereals. None are as high in thiamine as oatmeal. Also, oatmeal provides other B-complex vitamins. Its mineral content, especially of iron and phosphorus, rates it among the leaders.

Its delicious taste and easy digestibility further qualify oatmeal as an ideal "habit food" for a sensible breakfast.

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***WHEN THE DAY'S CALORIE ALLOWANCE IS**

1400 CALORIES OR LESS PER DAY

Breakfast
Approximately 300 Calories
Orange juice, 4 oz.
Oatmeal, 1 oz.
Skim milk, 4 oz.
Sugar, 1 tsp.
Toast, 1 slice
lightly buttered
†Coffee without cream or sugar

†For children substitute 4 oz. skim milk

2400 CALORIES PER DAY

Breakfast
Approximately 500 Calories
Orange juice, 4 oz.
Oatmeal, 1 oz.
Milk, 4 oz.
Sugar, 1 tsp.
One egg
Toast, 2 slices
with butter or jelly
†Coffee with cream and sugar

3000 CALORIES OR MORE PER DAY

Breakfast
Approximately 700 Calories
Orange juice, 4 oz.
Oatmeal, 1 oz.
Milk, 4 oz.
Sugar, 1 tsp.
Two eggs
Bacon, 2 strips
Toast, 2 slices
with butter or jelly
†Coffee with cream and sugar

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smooth, sustained
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INDICATIONS: acute hypotensive state due to spinal anesthesia; hypotension from hemorrhage, cardiogenic shock, drug sensitivity, surgical complications; shock associated with brain damage or infectious disease.

'**ARAMINE**' is a superior new vasopressor agent. Patients in shock respond with increased glomerular filtration rate, renal blood flow and urinary output. 'ARAMINE' offers these advantages:

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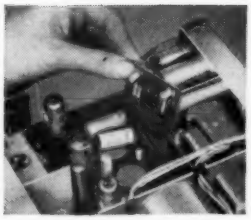
SANBORN MODEL 300

VISETTE

ELECTROCARDIOGRAPH



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4. Smooth and prolonged maintenance of blood pressure
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Supplied: in 1-cc. ampuls and 10-cc. vials (10 mg./cc.).

Reference: 1. *Circulation* **13:** 834, 1956.

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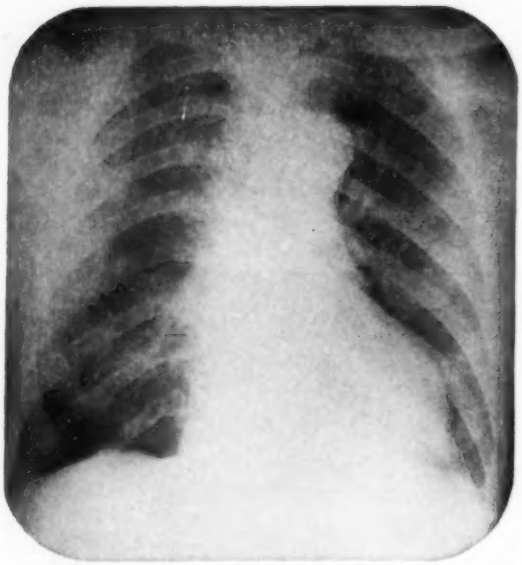


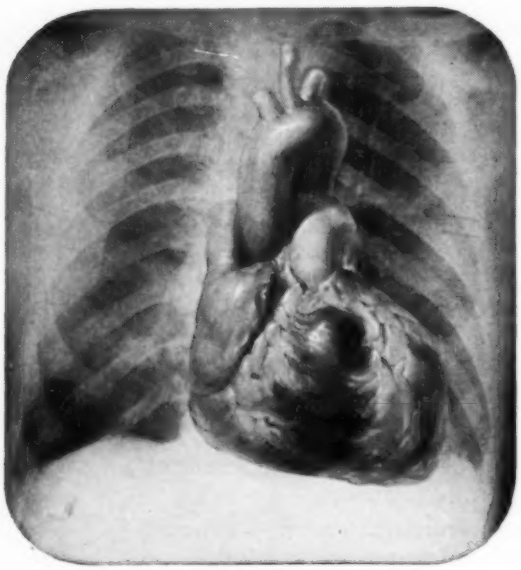
VISUAL HEART CLINIC—ONE OF A SERIES ARTERIOSCLEROTIC HEART DISEASE

ROENTGEN CONFIGURATION

Postero-anterior position

Moderate left ventricular enlargement with prominence and calcification of aortic knob.

Taken from White Laboratories' Technical Exhibit, American Medical Association, 105th Annual Meeting, Chicago, June 11-15, 1956.



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*HARRIS, R., AND DEL GIACCO R. R.: AM HEART J. (AUG.) 1956. BIBLIOGRAPHY ON REQUEST

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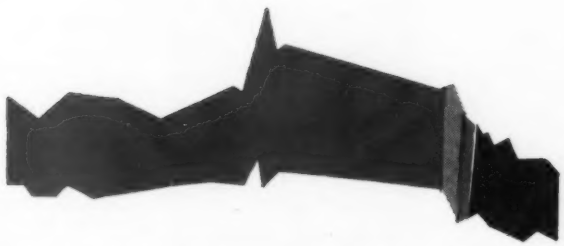

*Chart shows course of hypertensive patient over 3 1/2 years. Red area shows pressure before treatment—as high as 270/150. Black area shows response to Serpasil and Apresoline therapy. This favorable response to Serpasil/Apresoline was achieved with a maximum of only 100 mg. Apresoline daily, a dose so low as to virtually eliminate side effects. (Chart adapted from Wilkins, R.W.: Ann. New York Acad. Sc. 59: 36, 1954.) When blood pressure must come down, consider Serpasil-Apresoline combination tablets. Serpasil®-Apresoline® HCl (reserpine-hydralazine HCl CIBA). **C I B A** Summit, N.J.

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REFERENCE: (1) Ridolfo, A. S. & Kohlstaedt, K. G., "A simplified method for the rectal instillation of theophylline"—to be published

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The Interpretation of the
UNIPOLAR ELECTROCARDIOGRAM

by

GORDON B. MYERS, M.D.
Professor of Medicine
Wayne University College of Medicine
Head, Department of Medicine
City of Detroit Receiving Hospital

164 pages (8½″ × 11″)
Price, $4.75

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A.
Introduction.
The Relation of the Electrocardiographic Deflections to Mechanical and Electrical Events in the Cardiac Cycle.
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* * *

C.
Origin and Form of the Normal and Abnormal QRS-T Complex.
* * *

D.
Disorders of Rate and Rhythm.
* * *

E.
Summary of QRS-T Patterns in Unipolar Thoracic and Limb Leads.

This work is the outgrowth of previous manuals prepared to supplement the Graduate Course in Electrocardiography given at Wayne University College of Medicine for many years. The objective is an organized presentation of the interpretation of the unipolar electrocardiogram. The only basic physics included is that considered essential to the interpretation of the tracing; controversial theories that do not contribute to clinical analysis have been omitted.

The analysis of the arrhythmias is made from leads that clearly display auricular as well as ventricular deflections; the interpretation of the QRS-T complex is based upon the findings in multiple precordial and back leads, supplemented, when necessary, by esophageal and unipolar limb leads. The registration of the normal and abnormal QRS-T complex is based upon concepts developed by Frank N. Wilson and associates and shown to be consistent with experimental and post-mortem findings. These concepts have been presented in detail and suitably illustrated with diagrams as an introduction to clinical analysis. Efforts have been concentrated on a systematic lucid description of electrocardiographic findings in an attempt to make reproduction of tracings unnecessary.

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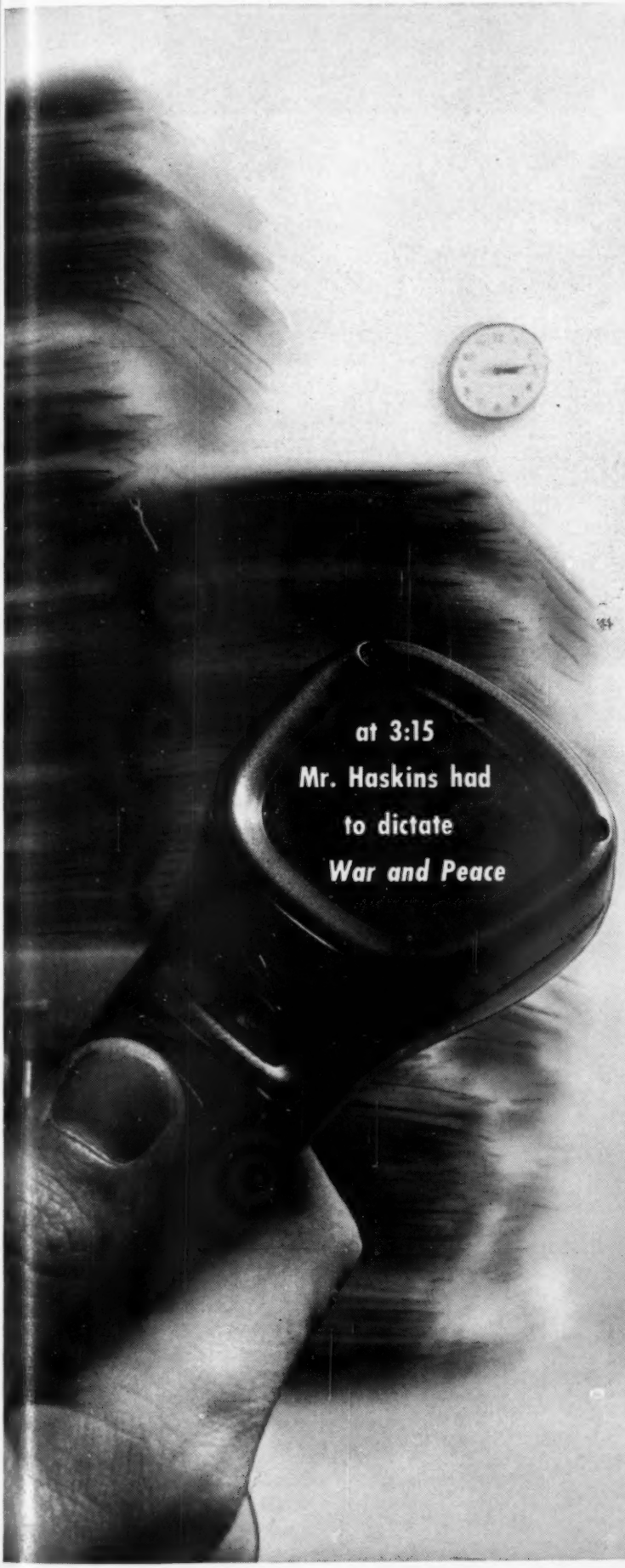

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1. Winsor, Travis: Comparative Effects of Various Rauwolfia Alkaloids in Hypertension; submitted for publication.

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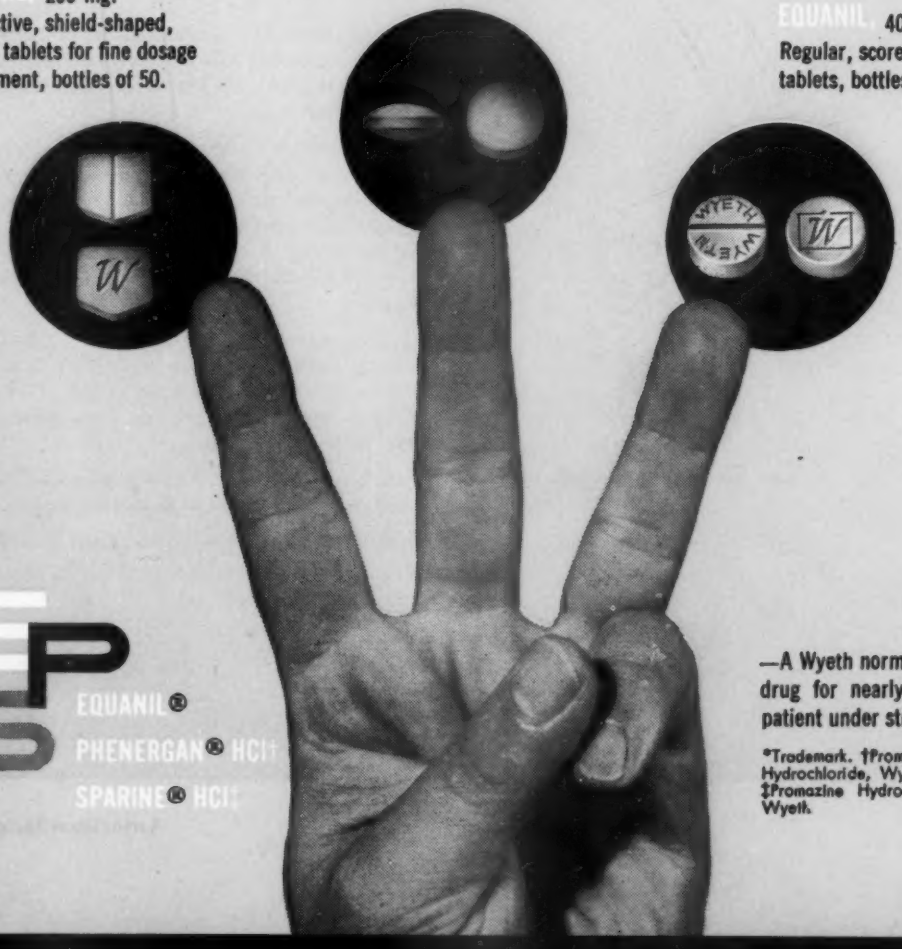

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1. Russek, H. I.: J. Am. Geriat. Soc. *4*:877 (Sept.) 1956.

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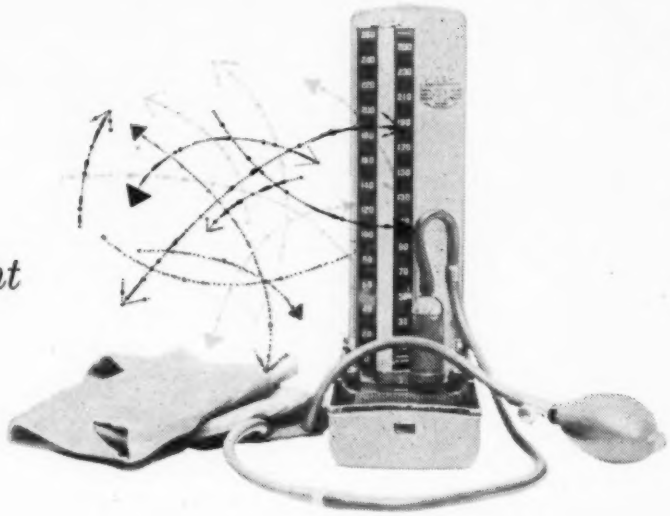

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1. Dunsmore, R.A., and others: Am. J. M. Sc. 233:280 (March) 1957.
2. Fulton, L.A., and others: Am. Pract. & Digest Treat. 8:1376 (Sept.) 1957.

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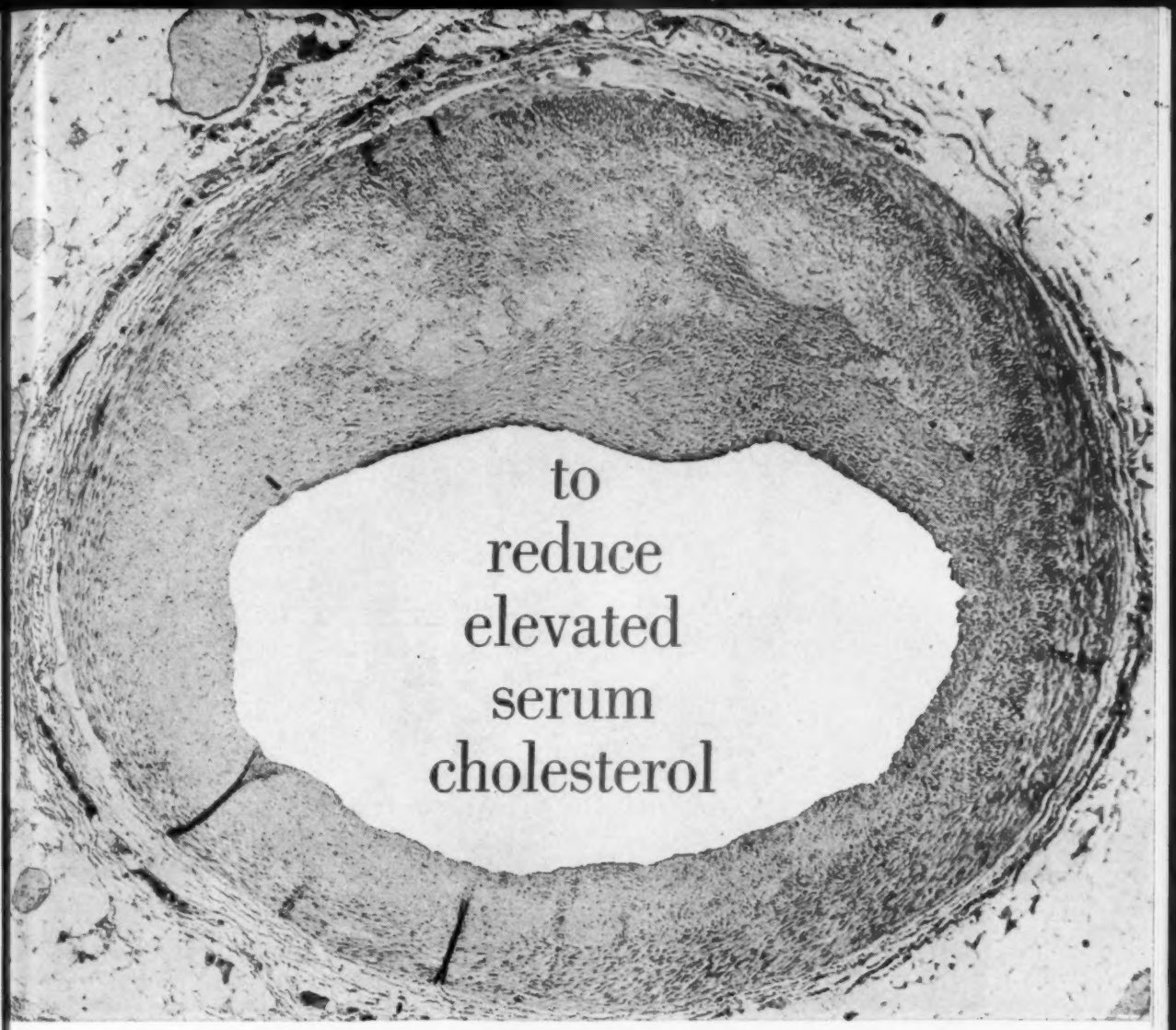

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1. Van Gasse, J. J., and Miller, R. F.: Current Concepts on the Etiology and Management of Atherosclerosis, Scientific Exhibit, American Medical Association Meeting, New York, June 3-5, 1957.

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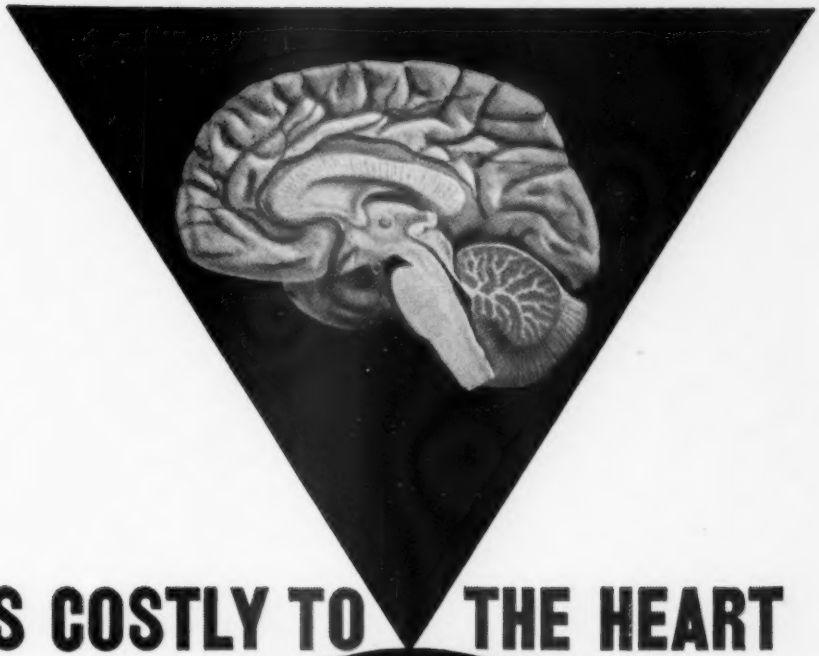

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*Waldman, S. and Peiner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.

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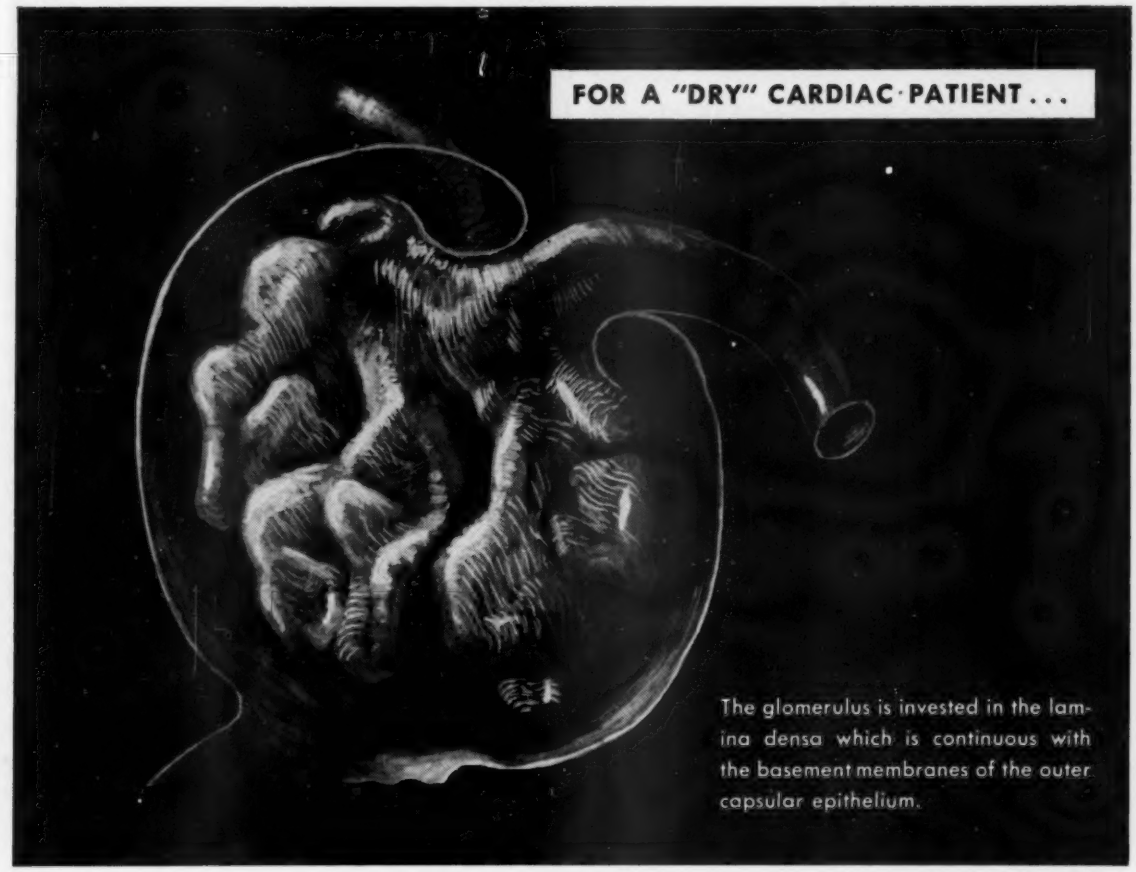
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1. Asher, G.: Personal communication, June 23, 1956.
2. Settel, E.: Rolicton® (Aminoisometradine), a New, Nonmercurial Diuretic, Postgrad. Med. *21*:186 (Feb.) 1957.
3. Goldner, M. G.: Personal communication, June 29, 1956.

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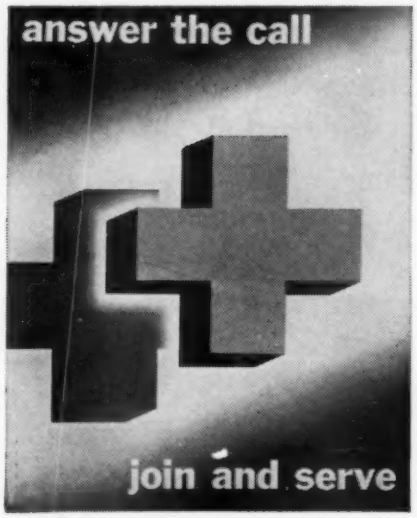

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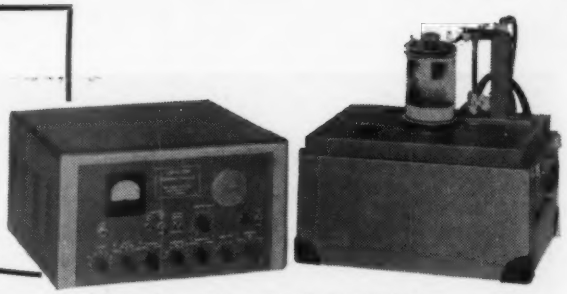

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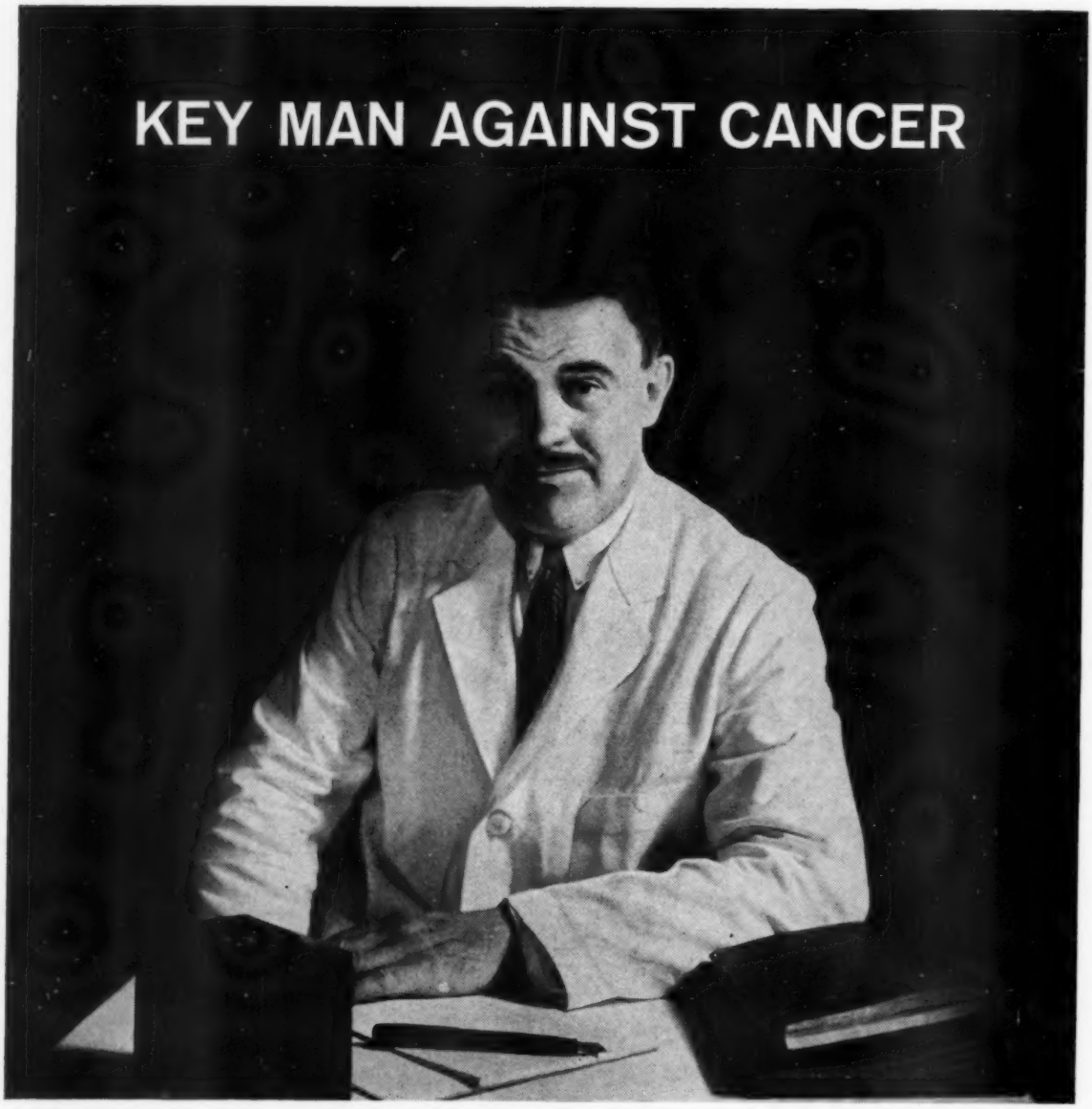

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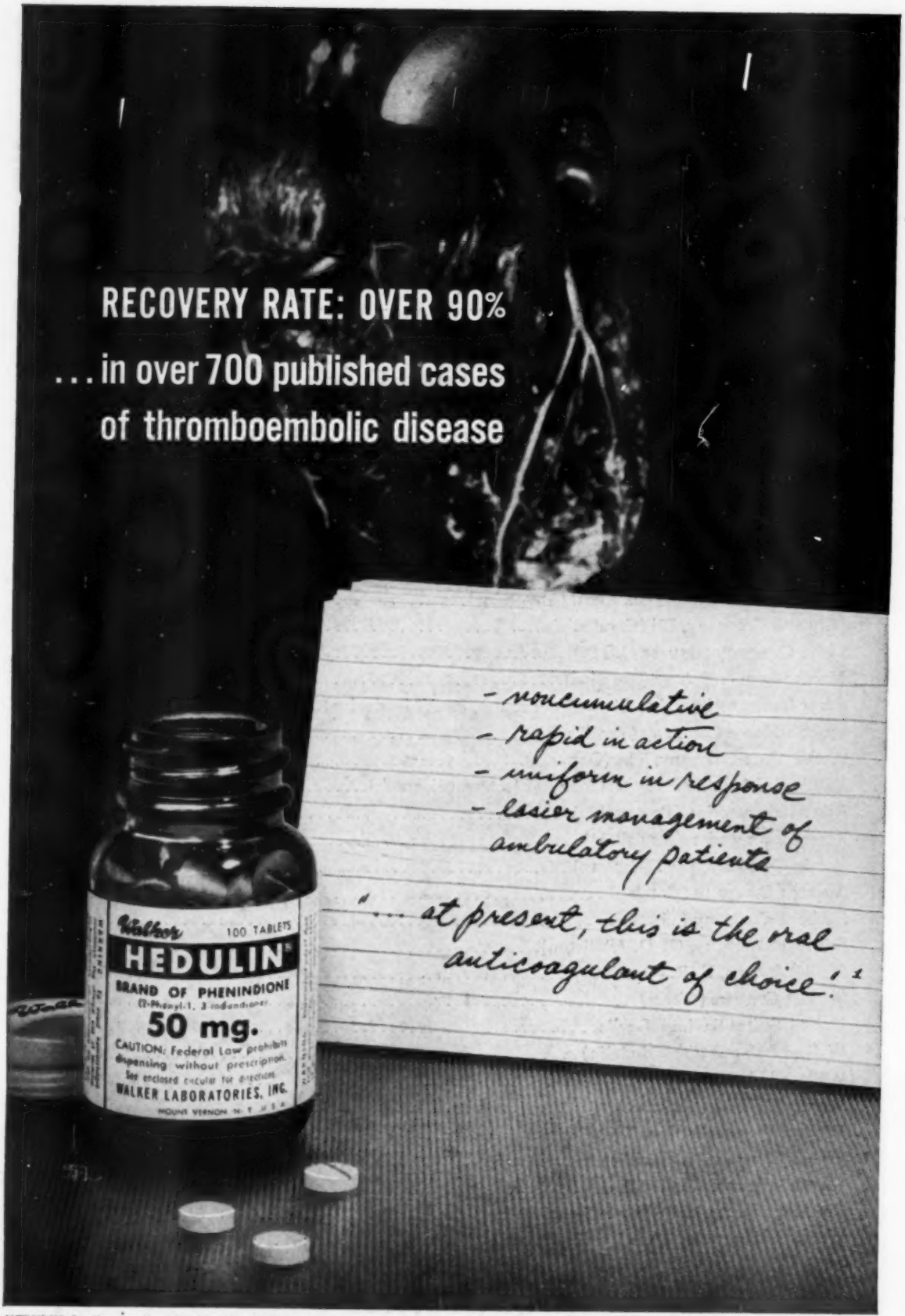

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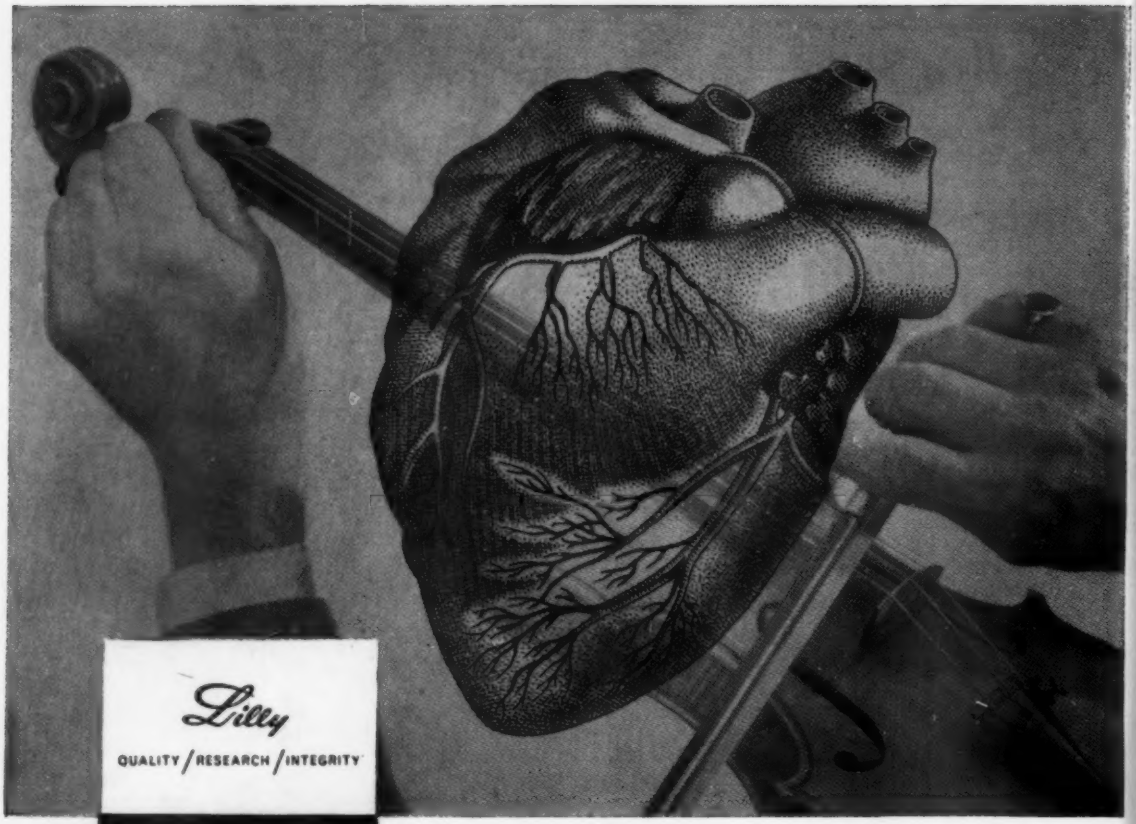

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